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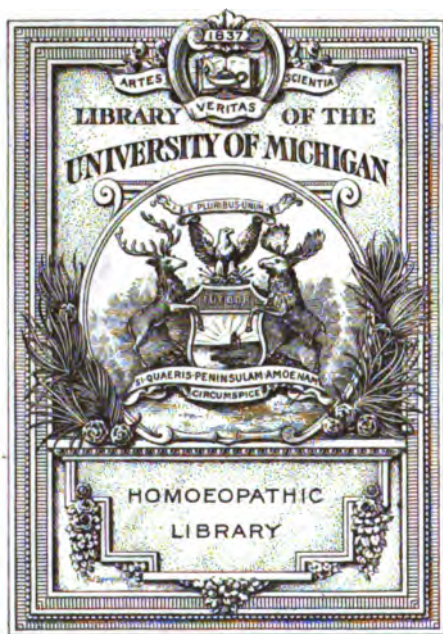
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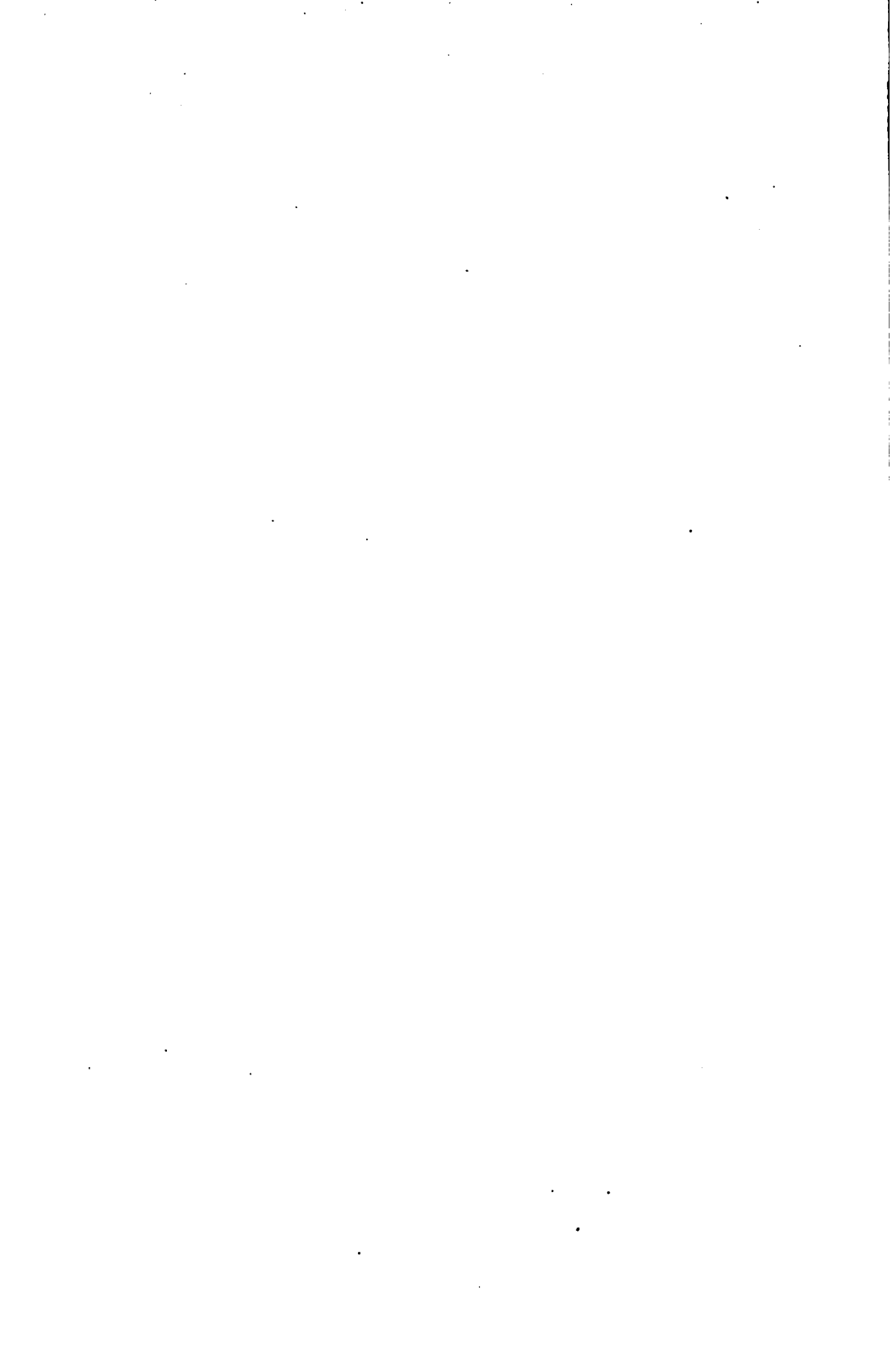


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HANDBOOK

OF

PHARMACOLOGY

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AMERICAN MEDICAL ASSOCIATION,
ETC., ETC.**

**WITH SEVENTY ILLUSTRATIONS. INCLUDING
MANY NEW AND IN COLORS**

NEW YORK
WILLIAM WOOD AND COMPANY
MDCCCCXIV

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THE QUINN & BODEN CO. PRESS
RAHWAY, N. J.

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PREFACE

The time has arrived in the differentiation of the teaching of medicine when the demarcation line should be more sharply drawn between those courses presenting to the student the scientific principles underlying the action of medicinal agencies and that phase of his training which deals with the practical use of medicaments in the alleviation of diseases. A parallel, illustrating the matter, can be drawn from the relations of the subjects of Physiology and Pathology. Physiology undertakes to present the underlying principles governing the reactions of the normal living body. Pathology deals with the reactions of the living body, but under conditions which we loosely classify as diseased, i.e., the reactions of the body when out of normal relations. Both treat of functions, but the two subjects are separated by the inherent nature which classifies one as normal functions, the other as pathological, a line which, of course, cannot be sharply drawn. Just so is it with the broad subject which deals with the reactions of the living body to drugs. The principles underlying this field are best presented from the standpoint of the reactions of the normal body to drugs and drug agents, which is the peculiar province of Pharmacology. The term Therapeutics, in the restricted sense, ought to apply only to that phase of the subject which deals with the reactions of the diseased body to drugs and drug agencies. These two phases of the broad field of Pharmacology and Therapeutics are, of course, intimately related, just as are Physiology and Pathology. And in the pedagogy of medical education they should be kept in their proper sequence, but should be presented in distinct and consecutive courses, as in the instance of Physiology and Pathology. Medical students should have placed in their hands a Textbook on Pharmacology without being burdened and confused by a mass of matter on practical Materia Medica and Therapeutics while they are getting the principles of the subject of Pharmacology.

The desire to carry forward this idea in meeting an organization which has already been well established in the medical curricula of our best schools has led to the presentation of this Textbook.

Courses in Pharmacology have been organized along two lines: One represented by that splendid old *Textbook on Therapeutics and*

Pharmacology, by George B. Wood, which ran so many editions in the hands of his descendants. This is typical of the group which classifies the drugs primarily according to the physiological symptoms they induce in the body. This classification, which characterizes a number of pharmacologies of the present, has in an introductory course the pedagogical disadvantage of presenting a confusing array of new facts to the student each time he shifts from one general topic to another. For example, under the chapter on Cardiac Stimulants, the student is suddenly brought face to face, not only with the great number of drugs, new and strange to him, which have this characteristic action on the cardiac apparatus, but he must correlate their actions throughout other parts of the body, making the problem doubly complicated.

The other type of Textbook, of which Cushny's classical *Pharmacology and Therapeutics* is our best example, bases the organization on the twofold nature of pharmacological agencies, viz., the chemical relations of the drugs and the characteristic physiological reactions of particular groups. No method can be strictly logical in presenting such a wide range of facts without involving wasteful repetition. But Cushny's method has the pedagogical advantage which may be illustrated by the subject of strychnine. Here the student is presented with the characteristic actions of a single new drug typical of a group. But he is asked to trace the reactions over the entire body with the physiology of which he is assumed to be familiar. In short, the student is asked to establish the scientific relations of a new substance or a group of substances within an organism with which physiology has already given him a working acquaintance.

In gathering the material for this book, use has been made of the literature of physiology, pharmacology, and therapeutics to the extent called for in the presentation of the underlying principles of the subject. Recognizing that even the most elementary student often desires fuller detail of some phase of the subject, and that the teacher needs a ready reference to sources in the literature used to support given principles, a few references to original sources have been inserted as footnotes. The articles so referred to are, in the main, those which present reviews of the literature or through which the literature may become available. No attempt has been made to give exhaustive reference lists. Free use has been made of the standard textbooks and encyclopedias of the subject, to the authors of which the writer expresses his particular obligation.

It is hoped that the number of figures introduced from the litera-

ture and from experiments in our own laboratories will be of special aid to both the student and the teacher. They are presented as standards for comparisons in laboratory experimental work as well as for the purpose of elucidating the subject matter of the text itself. For many of these illustrations I am especially indebted to my own students, to whom I here make grateful acknowledgment.

CHAS. W. GREENE.

COLUMBIA, MISSOURI.

September 10, 1914.

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CHAPTER I.

PHARMACOLOGICAL FACTORS OF GENERAL BEARING

I.

Introduction.

Pharmacology is the science which treats of changes in the physiological actions of normal living organisms induced by chemical or physical-chemical agencies. It must be understood that the word has often received a wider range of application in the literature, especially by the older writers. The term Pharmacology has been used synonymously with the term *Materia Medica* in its broader sense, also to designate the broad field of actions induced in pathological as well as in normal organisms. The present tendency in these days of specialization is to restrict the boundary of the field. In this book the term pharmacology is used in the restricted sense expressed by the definition just given.

Pharmacology, from this point of view, is not limited by any question of utility or application in the art of healing. It is quite immaterial whether a given agency be destructive of life, or of aid in maintaining life. If the agency is one that primarily influences the otherwise normal physiological processes, inducing reactions that are characteristic and constant, then it belongs to the field of pharmacology.

No sharp and all-inclusive boundary can be set around pharmacological agencies. Schmiedeberg has given a classical definition in which he specifically excludes substances capable of assimilation. Yet many recognized food materials have a decided influence on the normal reactions of the living body. They may be primarily nutritive, yet at the same time they produce changes in the physiological functions over and above those of simple nutrition, hence to that extent are pharmacological in nature. Also, many chemical agencies, which are well recognized as of the pharmacological group, for example alcohol or strychnine, are oxidized in the body and thus yield energy, and are to that extent nutritive, therefore foods. Nutritive processes and those of the type indicated as pharmacological shade from the one to the other so that no sharp dividing line can be drawn.

Pharmacological agencies are, for the chief part, *chemicals*, i.e., *drugs*. Many of these chemicals are of practical value in disease. The art of the application of drugs in the modification of the processes of disease with the purpose of recovering the normal functions is known as *therapeutics*. This term also is used with widely varying meanings by different writers. Occasionally the word *therapeutics* is given the meaning which includes *pharmacology* as outlined above and vice versa. The term *drugs* should be restricted to designate chemicals of therapeutic value. In the restricted interpretation of the relations of this field pharmacology deals with the physiological action of chemicals on the normal body while *therapeutics* deals with the action of drugs on the diseased body. In *therapeutics* chemical agencies are used for the purpose of recovering the normal, i.e., in the art of healing. In *pharmacology*, on the other hand, the whole intent of investigations and procedures is for the scientific purpose of unfolding the reactions induced. That the net results of pharmacological investigation may or may not yield a body of facts of positive utility is wholly a secondary consideration, though in presenting the subject from the standpoint of the undergraduate medical student it is the commendable practice to choose those materials and drugs which are of most importance in the practice of the art of healing.

If the action of the drug is destructive of the living organism it is said to be a *poison*. The science which deals with the limited field of drugs with poisonous action is termed *toxicology*. It is a subdivision of pharmacology.

Formerly much attention was given to the source and preparation of drugs. These subjects are now of primary interest, chiefly to the manufacturer and professional pharmacist. The present tendency is to eliminate them from other than secondary consideration under the subject of pharmacology. However, the definitions and limitations of these subjects may be given here for the sake of a fuller understanding of the general field. *Materia Medica* deals with the origin, preparation, and composition of drugs. As many of the active drugs are derived from plant tissues, the special field of the study of drug-producing plants is recognized under the title *pharmacognosy*. The art of preparing and compounding drugs is known as *pharmacy*, and the skilled druggist who does the compounding is called the *pharmacist*. With the present great development in the manufacture and preparation of drugs and drug principles we are rapidly dispens-

ing with the services of the pharmacist, who formerly played so large and important a part in the preparation of medicinal agencies.

A study of pharmacology assumes a wide and intimate knowledge of the subject of physiology. It is only on the basis of such knowledge that one can build the science of pharmacology. Physiology deals with the intricate and complicated reactions of the living body to every change either in the internal or external environment. These changes are constantly shifting throughout the life cycle of the individual organism and these shifting reactions make up the sum total of the physiological life itself. When pharmacological agencies are introduced into the body or brought into contact with living protoplasm by whatever device, the living tissue or organism responds to their presence. In other words, the presence of the special agency is only one of the numerous factors which induce response in the living protoplasm. The study of drug action is, therefore, only a restricted portion of the field of physiology.

Modern science has taken up the questions of pharmacology with the same vigor and spirit of investigation which has characterized the development of physiological knowledge during the last three-quarters of a century. In this spirit scientists have studied the details of the changes induced by drugs, thus establishing the facts on a strictly scientific observational basis. This method and the results are in direct opposition to the old empiricism. The findings have been seized upon by the clinician and therapist, since they enable him to proceed in the light of definite and known pharmacological actions of the agent. On the assumption that a given drug, which has been proved to induce a change of a certain nature in the normal organism will induce a change in the same direction in the diseased or pathological organism, the clinician can apply a given drug with a definite knowledge of what effects may be expected. This is the *rational* treatment in opposition to the *empirical*. Modern medicine and modern therapeutics look to the science of pharmacology for the basic facts for a rational procedure.

II.

The Nature of the Action of Drugs.

The chemical substances that produce pharmacological reactions in the body by virtue of chemical combinations with constituents of the body are properly called *drugs*. The term is an old and con-

venient one, though its application is often vague and indefinite. The character of the change in the reactions depends upon many environmental conditions, of which one of the most important is the manner in which the drug is brought into contact with the tissues of the organism. On this basis the drug actions may be either local or general.

1. **Local actions.**—A certain class of changes produced in the body by drugs is dependent upon the fact that the chemical is brought into contact with only a restricted part of the body, hence the restricted action is purely local and for purely mechanical reasons. For example, if strong sulphuric acid comes in contact with the skin it will produce chemical destruction of the tissue of that local spot. While sulphuric acid is generally destructive to protoplasm, in this instance it can act only locally in the same sense that a hot piece of iron will sear only that portion of the body which it touches.

2. **General actions.**—On the other hand, when chemical agents are introduced into the body in such manner that they are distributed throughout its extent by means of the circulation, then the reactions that occur are characterized by two general types.

The drug may be one capable of inducing change in the physiological activities of the body whatever the nature and function of the organs or parts considered. If so, it is said to have a general action. An example is found in alcohol. When alcohol is absorbed into the circulation and distributed throughout the organism it induces a change in function in all parts of the body.

Most of the drugs used in practical medicine belong to this class. It cannot be said that the chemicals produce exactly the same change in every type of protoplasm, yet the parts of the body affected are so numerous and widely distributed that the general functions are thrown out of balance, hence the action of the drug is said to be general in its nature. The majority of the physical-chemical changes induced in the body are of this class, especially the purer examples of salt action.

3. **Specific actions.**—In sharp contrast with these drugs of general action is a different class, namely, the *specific* drugs. In this class, although the drug may be brought in contact with all the tissues of the body still it shows especial affinity for certain tissues only and not for others. Nicotine is an example of such a drug. This alkaloid picks out especially the nervous tissue. Its specific action is still more detailed in that it forms compounds with that differentiation in nerve tissue represented by the link between the pre- and post-

ganglionic neurons of the autonomic system. While nicotine does enter into reaction to some extent with other portions of the nervous tissue and with the muscular tissues, still the intensity of the action is so much stronger at the particular synapsis that the other reactions are overshadowed, thrown into the background as it were. Hence this nicotine reaction is said to be specific. Numerous illustrations of this action can be given. Pilocarpine, acting at the same point, would be antagonistic to atropine, the characteristic curare action on peripheral motor nerve endings, the action of strychnine on certain synapses in the central nerve axis, and of caffeine on muscle and on nerve, particularly the nerve structures of the higher centers are examples. The behavior of such drugs in the body is always in sharp contrast with those reacting generally throughout the body such as the general protoplasmic poisons. The latter class are characterized by the changes which they induce in the physiological responses of general, i.e., undifferentiated, protoplasm. The specific drugs are characterized by the selective action on highly differentiated points in the structure of the animal body.

4. Indirect action of drugs.—Drugs also induce many changes in the normal functions of the body as *indirect actions*. That is to say, as a result of the primary action of the drug in the body the balance that exists among the coördinated physiological mechanisms is upset, hence there will follow a chain of effects induced by the shifting in the function of that tissue especially influenced by the drug. These purely secondary effects are physiological rather than pharmacological. Nevertheless they must be understood by the pharmacologist, and especially by the therapist who makes a rational application of the drug in disease. A simple illustration of this kind of secondary effect is found in the change of the heart rate produced by atropine. This drug paralyzes the endings of the vagus in the heart, thus eliminating the tonic control of the vagus. As a result the heart rate is greatly increased, not due to any direct effect of the drug, but purely secondary to the action of the drug in eliminating the inhibitory function of the vagus nerve. In like manner many drugs which produce profound changes in the circulatory system are accompanied by secondary effects on the respiratory mechanism or the renal system. Most so-called “tonics” induce their favorable changes in nutrition and metabolism in a purely indirect or secondary way.

III.

Relation of Pharmacological Action to Chemical Composition.

When drugs are introduced into the body they produce changes that are in nature either physical-chemical or chemical. In either case the type of reaction will depend in large measure upon the chemical composition of the drug itself. If the drug is of such chemical nature as to produce only physical changes, such as changes in osmotic pressure, etc., then its influence on the physiological behavior of the organism will be limited to the class of phenomena characterized by a disturbance in surface tension, osmotic equilibrium, etc. If, on the other hand, the chemical nature of the drug is such as will react with the protoplasmic constituents to form new or unusual chemical compounds, then the reactive power of the protoplasm will be altered, owing to the change in the chemical composition of the protoplasm itself.

Physical-chemical changes in the body may be induced in a number of ways, for example the digestive enzymes acting upon the food in the normal process of digestion produce hydrolytic changes in which there is an increase in the molecular concentration in the digesting mass. This condition alters the osmotic equilibrium as between the digesting food and the lining tissue of the alimentary tract. The physical result is an enormous increase in the interchange of particles as between these two substances, i.e., the foods and the mucous membrane. The cleavage products of the food will pass into the alimentary epithelial lining in relatively large numbers constituting the process of absorption. If, however, the content of the alimentary tract consists of such substances as magnesium sulphate which readily go into solution, but which permeate the lining cells with difficulty, then the osmotic balance will result in the passage of large quantities of water into the alimentary tract, thus greatly increasing the total mass and its fluidity. Such actions are purely physical-chemical.

Chemical changes, especially in those drugs that act specifically on the protoplasm of the organism depend upon a chemical reaction between the drug and some portion of the protoplasm of the living tissue. The chemical composition of some of the drugs has not yet been determined, but the greater number of pharmacological agents have well-known chemical composition. On the other hand, the exact and detailed chemical composition of the protoplasm of the tissues of the body is not known. There are many physiological indications of a high degree of involved and complex differentiation between the

tissues. These are indicated by the numerous cytological methods of staining, as well as by the details of variation in phenomena of physiological reaction. But rarely can one specify what is the particular chemical nature of a given differentiated portion of the living body by virtue of which it is capable of executing its characteristic functions. Nevertheless, we do not doubt that drugs induce changes in physiological reaction by a process of chemical reaction. Ehrlich has advanced a widely accepted hypothesis in accounting for the specific effect of toxins and anti-toxins. He and his followers have developed an elaborate artificial scheme to explain the type of reaction of substances of this class. Many different groups of drug actions can be explained along similar grounds, namely, on the assumption that some radical in the protoplasm combines with the drug or some portion of the drug. The new compound changes the nature of the protoplasm with the result that its physiological possibilities are altered.

IV.

Physiological Factors Modifying Pharmacological Responses.

It is evident that the reactions produced by a drug in the body do not depend altogether upon the chemical nature of the drug. The structure of the protoplasm in an animal, especially in the higher mammals, is more complex from the standpoint of chemical structure than any known drug. One only has to consider for illustration the enormous differentiations among animal species, differentiations which are slight from the individual point of view, but collectively are sufficient to give the characteristic specific qualities.

In a similar manner the individuals of the species or races of man himself owe their individual characteristics to variations in protoplasmic composition throughout the body. These variations are most obviously expressed through morphological characters, but a closer analysis shows that a morphological differentiation is only the machinery for an even more subtle physiological differentiation. Even from this broad point of view it is obvious that the responses which one individual will give to a drug are not, in fact cannot be exactly duplicated in another. The details of this phase of the subject can better be appreciated by considering specific factors.

1. **Age of the protoplasm.**—Of all the physiological characteristics influencing the pharmacological reaction of protoplasm age is one of the most important, second only perhaps to that of species. A young individual possesses different capability from the adult, whether

we make the application to man or to species of lower animals. If one considers a child, for example, at the time say of birth, there are several factors of which the following are important. First of all the differentiations of the body are incomplete at this stage, therefore the interrelations of pharmacological responses are not to be too strictly compared with those of an adult. Detailed changes in susceptibility of the central nervous system to recognized stimulation, such as characterize the adult, cannot be wholly reproduced at this age, hence the detailed variations in responses induced by a drug such as caffeine vary widely from those induced in the adult, a variation which may be compared qualitatively with the differences in response. An even more important factor is found in the greater susceptibility of young protoplasm to biological change in character as between adult man and the lower animals. Classical experiments in biological fields in recent years have fully emphasized the fact that young protoplasm is strongly imbued with the "impulse to growth." This characteristic overshadows the dynamic processes of adult protoplasm. Reactions of the young are to that extent different in nature. It is obvious that the responses to special conditions such as an environment of drugs will to such extent be fundamentally modified.

Among other things young protoplasm is quantitatively, i.e., weight for weight, much more susceptible to drug action. In performing experiments on animals or in the practical use of drugs in therapeutics this fact has long received recognition. In dose tables allowance has to be made, not only for the smaller proportionate size of the young in comparison with the adult in computing the adequate dosage (which is always figured for the adult), but for the difference in susceptibility of the child in comparison with the adult. Physicians in practical therapeutics have undertaken to express this relation in formulæ for computing the dosage for children which shall take into account both age and weight. Young's formula, which is widely used and is sufficiently accurate for all practical purposes, computes the dosage for a child as follows: The fraction obtained by dividing the age of the child by the age plus twelve gives the proper part of the adult dose to be given, i.e.:

$$\text{Young's formula,} = \text{The adult dose} \times \frac{\text{age}}{\text{age} + 12}.$$

A year-old child would receive, $\frac{1}{1+12} = \frac{1}{13}$ of the adult dose, or a

four-year old child $\frac{4}{4+12} = \frac{1}{4}$ the adult dose.

Children under one year, i.e., infants, must receive even smaller proportionate doses. Fried's rule, applying to this age, is: The dose for the adult \times the age in months \div 150.

Age susceptibility cannot always be figured in terms of formulæ. It is well known that young children are peculiarly susceptible to certain particular drugs. These can only be known through the process of experience.

2. **Race and species differentiations.**—As it is with age susceptibility so is it with species or race susceptibility. The very foundation of specific or race variation either in man or animals is expressive of protoplasm deviation in composition of a nature which leads to dissimilar responses to chemical agencies. Although many of our pharmacological tests are made on the common house animals, the cat and the dog, it is well known that these two animals give quite different responses to certain particular drugs, for example morphine. When weight and age and other individual characteristics are taken into account still there remains this qualitative difference, which is racial or due to species. The same type of variation is met with in the different races of man. The colored race, for example, is more susceptible to certain types of toxemia than the white, and vice versa.

3. **Individual susceptibility among both man and animals.**—A wide range of individual susceptibility to drugs has been noted. Some individuals are especially responsive to certain particular drugs. For example, now and then will be found a person who is peculiarly responsive to the alkaloid strychnine. Even the small quantity of this drug customarily given in the form of a tonic to the average individual, will be sufficient to produce incipient tetany in a highly susceptible individual. This characteristic rests on some form of differentiation in the protoplasm. It is met with in common experience in the fact that one individual may be unable to take milk in his food, another strawberries, or honey, etc.

The opposite of this type of variation is found in individual tolerance. Great variations are found in the ability of individuals to throw off the particular action of certain drugs. In common experience the most widely known of these reactions is that of tolerance to alcohol and to nicotine. While certain individuals are intoxicated by minute quantities of alcoholic beverages others can take relatively large quantities without marked evil effects. The particular cause of these variations among individuals cannot now be stated as it still belongs in the realm of the unknown, and for that reason we are in

position to give it a special name, namely *idiosyncrasy*. This type of variation, however, rests on an inherent variation in the nature of the tissues of the individual concerned. The term *idiosyncrasy* is not used to express that type of susceptibility or of tolerance which is acquired by repeated experience.

4. **Sex susceptibility.**—Sex characteristics are generally stated to be a factor influencing susceptibility to the action of drugs. Though not always admitted, it is currently stated that women require smaller doses of therapeutic agents than do men of equal size. This differentiation is, doubtless, to some extent, the same in character as that represented by species differences, though they are more specifically physiological. The physiological life of women is subject to periodic disturbances in poise and under these particular conditions there is often a greater response in the reaction to particular drugs. In the nervous system, in the glandular system, and especially in the urogenital system which is correlated particularly with the sex development, we have differences which influence the quantitative reaction of drugs. The more subtle sex differences which have long been recognized probably rest not so much on mass differences as on the variations in correlation between the organs of the general bodily functions as influenced by the primary sex organs, chiefly through their internal secretions.

In pregnancy there is a very great disturbance of physiological equilibrium. The usual coördinations are thrown far out of balance by the physiological adjustments to the developing fetus and the enlarging uterus. The nerve reflexes are more delicately poised and are stimulated into action by less profound changes in the environment than usual. The responses to pharmacological agents are for these reasons greater. Drugs also pass from the mother to the developing child, whose tissues are more susceptible. A non-toxic concentration for the tissues of the mother may prove fatal to the child. The child in the uterus may also be profoundly affected by the secondary changes in its nutritive condition, superinduced by the primary responses of the respiratory or circulatory systems of the mother, for example in surgical anesthesia.

Preceding and during the *menstrual period* there is great disturbance in the interrelations of the physiological reaction. Drugs displayed at this time produce effects somewhat differently co-ordinated in comparison to the effects ordinarily and normally called forth. The state of the body is comparable to that under many conditions of disease and the question of reaction variation is essentially

one of practical therapeutics. During that crisis in the life of a woman known as the *menopause* there are somewhat similar physiological disturbances that need to be taken account of in the interpretation of pharmacological reactions.

5. **The influence of mass, i.e., proportionate weight of active tissue.**—In the display of drugs in the human body it is found that, other things being equal, there is a response proportionate to the mass of active protoplasm involved. Two individuals of similar type and build, but of dissimilar weights require dosages proportionate to their weight, if equivalent responses are expected. However, weight in itself is not a sufficient guide. Adipose tissue is inactive tissue, hence variation in weight due primarily to adipose tissue must not be taken into account in determining dosage. It is only the active protoplasm that one can assume gives rise to drug reaction. If, however, the particular drug is of such nature as to enter into solution in the inactive tissue, then to that extent it is lost from the possibility of reaction with the active tissue. In old age there is less active tissue weight for weight than in the younger adult, hence pharmacological dosage must be somewhat reduced.

V.

Nature of the Change Induced by Drugs in the Pharmacological Actions of the Body.

The human body is a highly differentiated mass of tissues and cells. The differentiation has resulted in two general types of structure, first, the generalized tissues such as the skin, connective tissue, bone, etc.; and second, the specialized tissues, i.e., the nervous tissue, muscular tissue, gland, etc.

The first class of tissues is characterized by the possession of protoplasmic properties which retain, to a relatively high degree, the general characteristics of living protoplasm. These are the mobile tissues, the tissues on which growth, repair, and metamorphosis depend. These are the tissues which enter largely into the pathological processes, i.e., inflammation, tumor formation, and metastases.

The specialized tissues are those that have modified widely from the general type for the effective accomplishment of some one or more of the special functions such as irritability and conductivity in the nervous tissue, contractility in the muscular tissue, and secretion in glandular tissue. These are the tissues which are least easily modified in their form but which are most strikingly involved in the execution

of specific functions. They are the tissues which, when subjected to the influence of drugs, respond most acutely with changes manifested in the group by dynamic phenomena.

Of these two classes of tissue the first is involved in all those phenomena which are characterized by irritative processes. They are the tissues affected by such agencies as turpentine, arnica, dilute alkalies, iodine, cantharadine, etc. Those drugs which act upon the parenchyma, that is the specialized tissues, can produce, and do produce changes in the specific functions.

These changes are of necessity of two types, an increase in the function, i.e., stimulation, or a diminution of the normal function, i.e., depressive. Also, this possibility applies to each differentiated part of the body. Therefore the possibilities of change in the total functions of an organism are great in proportion to the number of highly differentiated tissues and dependent relations of tissues found in the body. As an illustration, when caffeine is introduced into the general circulation, it increases the functional activity of the nervous tissue by increasing the irritability of that tissue. Under the influence of this alkaloid a smaller stimulus will produce the same nervous reaction as that produced by a much larger stimulus in the normal body. The cerebral cortex is therefore more susceptible to stimuli, hence gives a greater amount of response to the same stimulus. The general activities of the body, as a whole, are proportionally increased or restrained, therefore, because this controlling tissue of the cerebral cortex is increased in its function. Or, if atropine is used in sufficient quantity to depress the activity of the vagus nerve endings, the usual stimulations, which increase the function of the vagus, will fail of their ordinary effects upon the heart. The delicacy of coördination, which is usually accomplished by the cardiac nervous apparatus, is lost owing to the blocking of conduction through the nerve endings. In a similar manner, when the ganglionic synapses of the autonomic system are under the toxic influence of nicotine, there will be a general depression of the delicacy of coördinative responses in the circulatory, respiratory, and glandular systems. Certain drugs, like the glucoside digitalis, increase the function of a large number of parenchymatous tissues at one and the same time. The intensive action of the drug is greater by virtue of this simultaneous action on numerous tissues. In a like manner the depressive action of morphine is greater because it lowers the reactive power of practically all of the tissues of the body.

VI.

The Method of Application of Drugs as Modifying the Changes in Pharmacological Activity.

The method of bringing the drug into contact with the body decidedly influences the character and the rapidity of reaction induced. It is possible to control the relative concentration and the sequence with which the drug is brought into contact with the different tissues of the body. One may exercise a certain amount of control over the rate and the degree of absorption, therefore the relative concentration of the drug in the different tissues at a given moment. The methods of presenting drugs to the tissues of man and mammals are briefly reviewed in the following paragraphs.

1. **Introduction of drugs by way of the mouth.**—This method involves the slow process of absorption through the walls of the alimentary canal and is, therefore, a relatively slow method of introducing drugs into the general system. As drugs, like the elements of food, are absorbed chiefly in the intestinal tract, it follows that the rapidity with which they are passed into the intestine will depend upon the general motility and sensibility of the alimentary tract, particularly of the stomach.

Drugs given by way of the mouth produce local effects in the mouth itself and in the stomach long before they reach the general system. All medicinal agencies with strong tastes and with positive odors sharply stimulate the sense organs of the mouth and nasal cavity. Reflexes are thus produced that induce secondary changes in the secretory, respiratory, and circulatory systems. Drugs taken by way of the mouth always reach the stomach and intestine in greater concentration than they will have after absorption. Thus strong alcoholic liquors, such as whiskies and gins, taken undiluted, produce marked local inflammatory processes in the stomach. After the slow process of absorption these alcohols are so far diluted that no general irritant effects occur, hence the characteristic general systemic effects alone are produced.

2. **The introduction of drugs by way of the rectum.**—The rectal method of introducing drugs rests upon the well-known fact that absorption takes place from this region. Even volatile substances, as ether, have been given by this channel. It has the advantage of avoiding the mouth and stomach, if for any reason such path is un-

desirable. The local reflexes produced in the mouth and stomach are avoided and the cardiac and vasomotor reflexes are not so strongly aroused. It is well known that artificial feeding may be accomplished by way of the rectum in instances of marked inanition or for other special reason.

3. **Hypodermic injection.**—A small syringe provided with a fine hollow needle tip provides a convenient and reliable method of giving drugs. Sterile solutions are injected into the subcutaneous tissues whence they are rapidly absorbed into the general circulation. This method has certain objections, i.e., considerable pain is produced by the mechanical effects of the injection and the pain induces complicating reflexes. Certain drugs are marked irritants and set up local inflammation at the point of injection, as for example digitalin. Finally, there is always the risk of infection by the introduction of contaminating germs.

Hypodermic injections may be used to secure the local action of drugs as well as to secure their general action after absorption. The best well-known illustration is that of cocaine. This general poison has proved of inestimable value in alleviating pain in operative and other procedures due to the successful hypodermic infiltration of the drug, care always being taken to prevent too rapid absorption so that a toxic quantity at any one time does not get into the general circulation. The hypodermic syringe is an invaluable instrument, not only in the determination of the facts of the pharmacological action of drugs, but in the control of drugs in practical therapeutics.

4. **Intramuscular injection.**—Meltzer has proved that a more rapid absorption of drugs occurs if the injection be made deep into the body of the skeletal muscles rather than into the subdermal connective tissues. This method, therefore, is to be employed in all cases where it is desired to introduce the drug in the most rapid way other than intravenous. This method is proving very valuable. By it drugs are rapidly, and, what is often of more importance, evenly introduced into the general circulation. Furthermore there is less pain and a slighter tendency to local inflammation from preparations that tend to irritation.

5. **Intravenous injections.**—The quickest and surest way of bringing a drug into contact with all the tissues is by introducing it directly into a vein. It thus passes throughout the whole circulatory system in a few seconds. Solutions are driven from a hypodermic needle or through a canula ligated into a vein. In either case precaution must be taken; first, not to introduce air and thereby produce

air emboli; second, not to introduce vigorous acting drugs too rapidly, lest they reach the heart in too concentrated form and lead to undesirable reactions before general distribution is accomplished; third, when either of these methods is practiced on man, or on any animal when the life is to be conserved, the whole procedure should be under aseptic conditions.

6. Transfusions.—The transfusion of blood from one person to another is a most valuable clinical method of saving life. It is practiced in cases of extreme anemia, or where there has been great loss of blood under conditions from which the individual does not rally. In this method an artery, generally the radial of the donor is directly connected with one from the recipient, and blood is allowed to run directly from the vessels of the one to the other. In transfusion we now know that only the blood of individuals of the same species can be safely transfused (see literature on Animal Sera, Toxins, etc.).

The method of transfusion is a reliable method of pharmacological testing as applied to animals. Valuable information as to the reactions of epinephrine, or sera, etc., has been secured by this method.

7. Inhalation and insufflation.—Everyone is familiar with the method of introducing volatile drugs by inhalation and insufflation as practiced in anesthesia. The volatile anesthetics, ether and chloroform, as well as the gases, as nitrous oxide, carbon dioxide, or the poisonous carbon monoxide, are readily absorbed through the lining epithelium of the lungs. They are taken up by the blood in the pulmonary vessels and quickly distributed to all parts of the body.

It is also possible to introduce substances which can be atomized and inhaled with the respiratory air. Such atomized particles come in contact with the pulmonary epithelium and are fairly readily absorbed. Volatile oils which are carried off on steam belong to this class of materials.

8. Local application of drugs.—A favorite method for bringing drugs into contact with particular parts of the body is that of local application. This method is chiefly limited to external surfaces of the body or those portions of the body that are readily reached through the external openings. Deeper portions of the digestive tract, such as the stomach and the rectum, admit of a limited application of drugs by this method. Also in hypodermic injections, as for example cocaine, drugs can be so manipulated as to produce strictly local effects.

One of the best illustrations of the local application of drugs is

that of atropine to the surface of the eye. The alkaloid is slowly absorbed into the tissues of the cornea and the underlying parts, where it ultimately comes into contact with the musculature of the iris and ciliary processes. In this locality the atropine penetrates to the nerve endings of the smooth muscles involved in the act of accommodation where it produces its selective toxic action. It is true the atropine is absorbed into the general circulation, but only very slowly, and it does not reach the general tissues in concentration great enough to produce noticeable changes in organs other than the eye. If an excess of atropine be applied to the eye and its application too long continued, then there may be enough absorbed into the general circulation to become active.

The method of local application is capable of wide use, especially in the group of irritants. Drugs that would be very toxic if introduced into the general circulation may be used by this method. Contact restricted to a local area, may still be associated with extensive and general physiological effects on the organism as a whole. These effects are, for the greater part, reflex in character, hence fall on the factor of coördination influences within the body. One of the chief values of the method of local application depends upon this reflex influence, an example of which is found in the reactions of the group of counter-irritants.

VII.

Changes Produced in the Reactive Power of the Individual by the Continued Application of the Drug—Summation and Tolerance.

If drug doses are given in succession, two changes may follow in the intensity of the physiological reaction produced. First, if the doses follow in too rapid succession so that elimination is incomplete there will be *summation*, or *cumulative effects*. This is illustrated by the usual therapeutic administration of digitalis. Mostrom and McGuigan¹ have explained certain increased sensitiveness of animals to strychnine as "habit," or as Sollmann² puts it "The system appears also to be subject to what might be called an 'education' to the effects of the drug."

However, the more striking and more common phenomenon is the

¹ Mostrom and McGuigan: *Jour. Pharmacology and Exp. Therapeutics*, Vol. III., p. 515.

² Sollmann: *Textbook of Pharmacology*, 2d edition, p. 131, 1906.

great decrease in susceptibility as the dose is repeated, known as *acquired tolerance*. Acquired tolerance differs from individual tolerance in that it implies an individual readjustment to the new agency. It is most strikingly illustrated in the instance of the numerous drugs that are abused leading to the formation of drug habits. The originally sensitive tissues acquire an immunity whereby the organism may withstand the toxic action of a dosage many times greater than the ordinary fatal quantity. This is illustrated by the widespread nicotine habit, so prevalent in America, or the opium habit of the Orient, or by the worldwide prevalence of the alcohol habit.

A few cubic centimeters of whiskey will produce incipient intoxication in an individual not accustomed to its use, whereas a confirmed toper may consume more than a pint or even a quart a day and still maintain his equilibrium.

The organism acquires tolerance in several ways. There is an actual decrease in the protoplasmic sensitiveness to the drug as in the case of nicotine. Or the presence of the drug may lead to the strengthening of the defenses of the organism expressed in the increased oxidative power as with alcohol, or, in the production of neutralizing substances as in the case of the toxins.

VIII.

Pharmacologic versus Therapeutic Action.

Pharmacological action is defined above as change induced in the normal physiological functions, whereas therapeutic activity is change induced in the pathological functions with the object of aiding the recovery of the normal. Rational therapeutics assumes that these two types of change are in the same direction, are alike in kind. However, pathological states induce great changes in an organism along two lines. There are changes in the protoplasm itself, and these are more or less responsible for changes in the interrelations of parts, hence in the functional coördinations. The diseased condition is the sum of these two classes of changes. Pathological protoplasm will not always give the same quantitative responses to a drug as does the normal, in fact there are certain qualitative variations as well. In general the response is of a similar quality, but varies more widely quantitatively. The greatest difference lies in the change in the type of responses in the great coördinative mechanisms. It is evident that familiarity with pharmacological action is a necessary foundation

for therapeutic applications. But the latter must take into consideration the changes induced by the pathological states produced by disease, hence the corresponding variations in the response to drugs. This field is now rapidly being brought to a more accurate scientific basis by the development of the newer field of experimental therapeutics.

IX.

The Fate of Drugs in the Body.

Drugs are disposed of by the body in several ways. Certain drugs, as alcohol or morphine, are largely oxidized by the tissues. From 90 to 95 per cent. of the alcohol of liquors is oxidized, leaving only a small percentage to be disposed of in other ways.

Excretion by the kidney, the skin, the lungs, in volatile substances, or by the alimentary tract is the usual fate of most substances. The material may be excreted unchanged or it may be partially oxidized and then excreted. Substances that are excreted by the alimentary tract are partially resorbed by lower divisions of the tube, hence their elimination by this route is through an ever-repeating circle and slow. Morphine is an example. It is excreted freely into the stomach and reabsorbed from the intestinal tract further on. The heavy metals, which form very fixed chemical combinations in the body, are dissociated and eliminated only with extreme difficulty and in minute quantities at a time through the kidneys or the alimentary tract. Most volatile substances are rapidly eliminated through the pulmonary epithelium and carried off in the expired air. Ether and chloroform are typical of this class.

The chief excretory channel for the great majority of drugs is the kidney, the substance being eliminated in solution in the urine.

PART I.
ORGANIC DRUGS.
A. General Depressant Series.

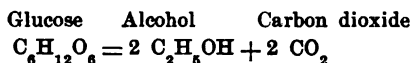
CHAPTER II.
THE ALCOHOL GROUP.

I.

Introductory and Chemical.

Introduction.—Of the alcohol chemical series the form most interesting from the pharmacological standpoint is ethyl-alcohol, C_2H_5OH . This alcohol is the particular constituent of a long series of fermentive beverages and has been known since the beginnings of history. The use of alcohol and alcoholic beverages in medicine also dates to the earliest known period. It does not seem necessary in this connection to trace the historical steps down to the present time in relation to either the medical or social use of alcoholic preparations. Perhaps it is sufficient to say that in the last few years the reactions of alcohol in the body have been studied both qualitatively and quantitatively in the light of our modern advances of physiology and physiological chemistry. The result has been to give this substance a much more rational position in the list of pharmacopeial remedies than it has ever known before.

Solutions and chemical relationships.—Ethyl-alcohol is derived from the fermentation of different sugars by yeast. The reaction that takes place in general can be represented by the formula:—



Absolute alcohol is a transparent, highly volatile substance with a specific gravity of 0.797. It boils at a temperature of $78.5^{\circ}C$. The ordinary commercial alcohol contains about 95 per cent. absolute alcohol.

The alcohols used in medicine are rarely pure alcohols. Instead

are used the alcoholic liquors, such as whiskey, wines, brandies, etc. Liquors contain a varying percentage of alcohol depending upon the particular class to which they belong.

Brandies, whiskeys, and rum	40-60% alcohol.
Wines	6-22% “
Beer	3-6 % “
Ales	2-5 % “

Liquors always contain a number of principles more or less volatile which bear a close chemical relation to or are developed during the fermentation of the alcohol. It is these substances that give the characteristic aromas and flavors peculiar to the different types of liquors. The development of the flavoring materials depends largely upon the type of yeasts fermenting the fruits and grains, but to some extent upon the character of the fruits and grains used. It is this characteristic of the local brews of liquors from special localities which is prized so highly by connoisseurs, as for example in the different Rhine or Spanish wines.

The alcohol series varies in toxicity or in intensity of pharmacological action somewhat in relation to the structural formula of the particular alcohol. In general it can be said that the intensity of the toxic action increases as we go up the aliphatic series. The toxicity of the first five members is as follows, according to Baer:

Methyl CH_3OH	Toxicity 0.8
Ethyl $\text{C}_2\text{H}_5\text{OH}$	“ 1.0
Propyl $\text{C}_3\text{H}_7\text{OH}$	“ 2.0
Butyl $\text{C}_4\text{H}_9\text{OH}$	“ 3.0
Amyl $\text{C}_5\text{H}_{11}\text{OH}$	“ 4.0

In the higher members of the series the solubility of the substances in the body fluids becomes relatively less and therefore the toxicity falls off, the paraffins being wholly insoluble and inert.

II.

Alcohol as a Local Irritant.

1. The local effects of alcohol on the skin.—When alcohol is applied to the skin at any point on the surface of the body in relatively concentrated form it produces a local irritative process in the epidermal tissues. Under ordinary conditions the alcohol evaporates before the irritation proceeds very far and the effect is

slight and evanescent. But if the alcohol is kept from evaporating, then the irritation may proceed even to advanced stages of inflammation. The alcohol itself penetrates the skin rather freely due to its solubility in the oils of the surface. As it comes into contact with the deeper layers of the epidermis it extracts water and tends to precipitate the cell proteins, changes that account for the inflammatory process.

The local action is twofold. In the first place, it produces a primary stimulative effect on the processes of repair and growth. If the primary action of the alcohol is intense enough there may follow in definite pathological sequence the changes which characterize the development of inflammation. In the second place, an immediate stimulation is produced on the nerve endings in the local portion of the skin. The result of the stimulation is a series of reflexes which may affect not only the local circulation of the part, but also the general circulation, and, in the more extreme cases, the processes of respiration and the general bodily movements. The secondary effects are of course not peculiar to or characteristic of alcohol only, since they are characteristic of any local stimulative agent.

2. The local effects of alcohol on the mucous membrane of the mouth and stomach.—Alcohol and alcoholic liquors produce distinct physiological responses when taken by way of the mouth. These responses are more marked with the liquors than with the pure alcohol, due to the fact that they contain esters and other volatile constituents which produce striking reflex stimulations.

The local effect of the strong alcohol as such on the moist mucosa of the mouth and of the stomach is much more irritative than in the case of the skin. These membranes have a higher water content and the living protoplasm is not separated from the alcohol by a thick layer of dead tissue as in the skin. Therefore, the changes produced are immediate and stimulative leading to marked nervous reflexes through the medullary centers. It is at this point that one can make the strongest claim for the clinically beneficial effects of certain classes of alcoholic liquors. The mild stimulation of the taste buds in the mouth, and of the olfactory membrane of the nose, produces secretory reflexes through the medulla which not only increase the secretion of saliva but also induce the primary secretion of the gastric juice in the stomach, and possibly also the secretion of the pancreas. The painful and burning sensation of the stronger alcohols in the mouth may set up to some extent the same reflexes, but they are not so normal or beneficial.

In the stomach the mild irritation of the mucosa produces some degree of reflex secretion of gastric juice, a matter that has been adequately determined by Chittenden. Undoubtedly the stronger alcohols, especially when oft repeated, produce more profound processes leading to inflammation and oftentimes to necrosis. The necrotic ulcers of the chronic alcoholic are sufficiently well known. Certainly in such cases the gastric mucous membrane has long since passed into a pathological state in which even a normal secretion cannot take place, much less the favorable physiological reflexes.

This local action of alcohol rests on its toxicity to general protoplasm. It is this factor which makes of alcohol a valuable antiseptic. Isolated organisms, such as bacteria, protozoa, etc., have their protoplasm precipitated by alcohol of sufficient strength and are therefore killed.

III.

Detailed Systemic Effects of Alcohol.

1. The action of alcohol on the central nervous system.—Alcoholic liquors have long enjoyed a popular reputation as stimulants for the nervous system. Experimental tests have been made which claim for alcohol in very moderate quantities some acceleration of mental reactions, when tested by psychological tests and methods. Yet, writers working under such stimulus have not consistently found an increased brilliance of their products judged under calmer conditions. The question can safely be considered as still in doubt as to whether alcohol in such quantities favors or hinders the process and reactions of the central nervous system, the phenomena of which are expressed in mental or psychical states.

It is generally admitted that larger doses of alcohol depress intellectual functions, and along with this depression will come marked changes in the general physiological reactions of the body. We are, in America at least, all too familiar with the details of the successive stages of the toxic effect of alcohol. However, some of the salient phenomena will be re-enumerated for the sake of clearness of discussion.

In the first stage or in mild alcoholic action the individual changes in his personal estimate of his activities. The drinker feels that he is more brilliant, whether or not he be so. There is a greater vivacity, especially in company, usually associated with de-

creased reserve and self-restraint. The individual has what superficially appears to be a keener appreciation of humor and wit, that is, he gives greater responses to these stimuli. He shows a tendency to much talking, to free laughter, and also to accelerated neuromuscular activities. The respiratory rate is generally somewhat accelerated, as is also the heart rate. An increased flushing of the skin, especially noticeable in certain portions of the face, is one of the first indications of mild alcoholic effects, an index which comes even earlier than those symptoms noted above.

In the second or successive stage of alcoholization there comes on a more marked degree of incoördination of mental processes indicated by less logical sequence of thought. This characteristic is shown in the responses to wit, humor, etc., i.e., in responses to social intercourse. Along with these symptoms there is an increasing lack of neuro-muscular control revealed by some unsteadiness of movement as indicated in the process of writing, in the movements of walking and the like.

With the still greater increase in the effects of alcohol there is a marked depression of the entire bodily functions. This is characterized by a progressive loss of muscular control to the point of narcosis, associated with increasing loss of normal reflex nerve reactions, a depressed respiratory rate, a slower heart, and inefficient circulation. In this stage, especially when much prolonged, there is a decided lowering of the general body temperature.

2. Explanation of the nervous symptoms induced by alcohol.—

Two schools have arisen for the explanation of the influence of alcohol expressed through the nervous system. These two schools are led by the two great pharmacologists, Binz and Schmiedeberg. Binz and his followers believe that the incipient effects of alcohol on the central nervous system, including the cerebral cortex, are actual stimulation, that the functions are really accelerated. They of course admit that the later effects are narcotic. Schmiedeberg and his followers, on the other hand, believe that the incipient effects of alcohol on the central nervous system are narcotic and not stimulative. They explain the phenomenon of apparent accelerated function by the view that the narcotic effect of alcohol is progressively toxic, beginning with the highest portions of the cerebral cortex and extending in a descending direction, a process that characterizes certain dementias and is known as dissolution. The higher processes of the association centers of Flechsig through which the processes of reasoning, of attention, and mental association are executed will be first attacked by alcohol

and, by Schmiedeberg's view, should be lowered in efficiency. Numerous later observers have found evidence to indicate that this assumption holds. Simple mathematical processes take place less readily when the computer is given a small quantity of alcohol. Also computations of distance as well as acuteness of perception are depressed. Typesetters do less work, i.e., place fewer type and with less accuracy, on days when they receive a small measure of alcohol.

The accelerations of simple motor processes, which in their most complex form are associated with psychic reflexes, are explained on this view by the elimination of the inhibitive regulative control which the psycho-motor centers receive from the higher centers of the cortex. In progressive alcoholism there will come, therefore, a time when the association centers will have been narcotized just sufficiently to depress their inhibitive regulative control over the basic motor centers. These centers, therefore, will be physiologically freer to respond to the incoming sensory stimulations of whatever kind. The resultant reflex motor responses will be greater. The alcoholic therefore talks more volubly, laughs more freely, and responds more strongly to the stimulations of his social environment. These increased responses are by this line of reasoning to be considered as evidences of lack of control rather than positive stimulation.

If one follows the progressive influence of alcohol in its intermediate and advanced stages he will note that the marked depression of function appears successively in certain nerve centers, and this order is surprisingly near the ranking one would make on physiological evidence when asked to classify these centers in a descending series. There is first a loss of psychological activities, perhaps even of consciousness itself. This is followed by lack of motor control, especially of the arms, legs, and vocal apparatus in which the complexity of nerve structure and function is unquestionably of later physiological development. Finally there is loss of function of the trunk musculature, therefore of the respiration, and a marked depression of the circulation, together with paralysis of those medullary centers controlling the same.

3. The action of alcohol on the nervous system of lower animals.—The general influence of alcohol on intelligence as expressed by the action of the cerebral cortex has been tested on dogs by Hodge of Clark University. He found decided changes in the mental characteristics of dogs, particularly indicated by a great increase of timidity and fear, the especial symptom of the neurosis in man. The evidence of intellectual power he tested in four dogs of the same

species, by the method of retrieving. Two alcoholics, that is dogs receiving a definite quantity of alcohol in their food each day, and two normals were used. These dogs retrieved a ball on the gymnasium floor. The alcoholic dogs were far less efficient than the normal. Of a series of 1400 balls thrown "The two normal dogs retrieved 922, the alcoholics 478. This gives the alcoholics an efficiency of 59.8 per cent. as compared with the normals." Of the two male dogs the ability of the alcoholic was only 32 per cent. of the normal. The pair of alcoholics "gave evidence of very much greater fatigue." Of course the greater efficiency of the normal dogs in these tests rests in part in physical agility and muscular endurance as well as on nervous characteristics.

4. The duration of the effects on the central nervous system.—

The duration of the effects of alcohol varies with the size of the dose. If the amount of alcohol has been sufficient to produce the second set of changes previously outlined, then the body will not recover its former degree of activity for some fifteen to twenty-four hours or even more. The duration of the change is longer than has generally been supposed. Experiments have been carried forward to prove these effects on quantitative work as well as on qualitative. Dynamometer experiments by which one measures the amount of muscular work given off in voluntary muscular contractions tend to show that the effects of alcohol are recovered from very slowly. Voluntary muscular effort has in it two factors, the nerve stimulation and the muscular response. The action of alcohol is not the same on the two tissues. Hence the results of this type of test have been a little confusing. Jacobi's observation, that an individual could more clearly estimate small differences in weight when under small doses of alcohol than in the normal state, can be explained on the ground that the muscle itself is rendered less stable by the drug. It was shown by Lee and Salant that muscles execute the simple muscular contractions more quickly when subjected to moderate quantities of alcohol. In Jacobi's experiment it is not necessary to assume an increased sensibility of the nervous part of the apparatus, i.e., of the motor centers.

An interesting observation was made by C. C. Stewart¹ showing that alcohol brought about a change in the amount of Nissl substance in the cells of the different portions of the brain, tending to diminish the content of the Nissl substance. Illustrations of the change in the pyramidal cells is shown by Figure 1. In light of later work on the structural changes in nerve tissue under the influences of

¹ Stewart, C. C., *Journal of Exp. Med.*, Vol. I., p. 623, 1896.

activity, drugs, etc., it is probable that this stage of change represents only a mild degree of acute activity quite comparable to that shown by vigorous activity of ordinary type. Whether or not alcohol produces the more profound changes observed under other conditions remains yet to be learned.

5. The action of alcohol on muscular tissue.—The muscular apparatus consists of the muscle fibers, the controlling motor nerves, and the nerve endplates which unite the two. The evidence showing the action of alcohol on the nervous tissue applies to the motor cells of the spinal cord and brain stem, though these cells are

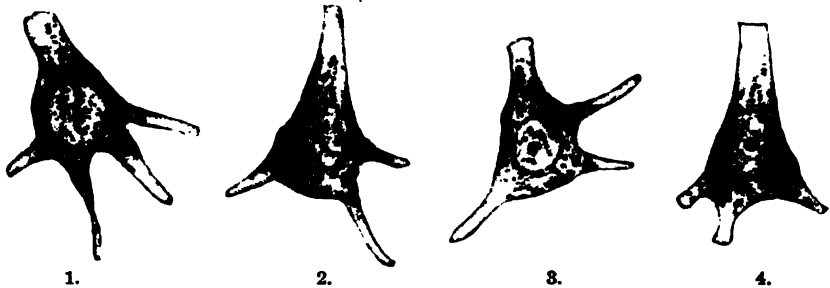


FIG. 1.—Alcohol on the amount of Nissl substance in pyramidal cells; 1, normal; 2, alcohol for 50 minutes; 3 and 4, alcohol for 54.5 hours. Stewart.

somewhat less sensitive than other portions of the nervous system. Nerve fiber itself can be narcotized by alcohol as has been shown by Waller, in this instance preceded by evidence of stimulation. Muscle has been studied extensively by Lee and Salant,¹ who showed that there is a distinct increase both in the sensitiveness of the muscle to stimulation and in the amount of work which a muscle will do under repeated stimulation. Also, the number of contractions which can be completed in a given time is greater, since the individual contractions are quicker. These three effects are observed only on muscle which has received a relatively moderate quantity of alcohol, preferably through the blood vessels. When the dosage is greater, then the reverse of the above effects is true. Lee and Salant compared the two gastrocnemii of the frog, one of which received alcohol, the other none. When after a mild injection of alcohol both are stimulated uniformly with single induction shocks repeated, say, every two seconds, which allows time for a complete relaxation of the muscle after each stimulus, and if the stimulation be kept up until the muscles are exhausted the alcoholic muscle will give off a

¹ Lee, F. S., and Salant, W., *Am. Jour. Physiol.*, Vol. VIII., p. 61, 1902.

greater amount of work than the non-alcoholic. Comparison of the two records shows that the alcoholic muscle lifts the same weight through a greater height and that the number of contractions is greater. On the other hand, if a strong dose of alcohol be used just the reverse results are obtained. The alcoholized muscle does the least work. These results, which have often been repeated and confirmed in our pharmacological laboratory, seem to prove that the muscle substance as such is a little less stable under the influence of a mild amount of alcohol. The decrease in stability permits a quicker response upon stimulation, a result that can be explained on the assumption of increased irritability.

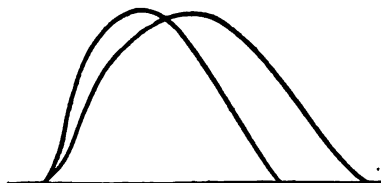


FIG. 2.—Curves of simple muscle contraction from the gastrocnemii of the frog. The quick contraction, after 0.08 cc. of 10 per cent. alcohol to 1 gm. of body weight. The slower contraction, the normal muscle before alcohol. Lee and Salant.

It would seem, therefore, that skeletal muscle as such may receive a true stimulation by alcohol. This is of little practical value, however, since all voluntary muscular activity calls for the nervous stimulating factor. Nerve cells have already been shown to be narcotized by alcohol. These two antagonistic effects upon the neuromuscular apparatus have served to suppress the real truth for each, and have led to confusing interpretations in many lines of experiments such as voluntary muscular work.

No evidence has yet been adduced showing any favorable influence of alcohol on smooth muscle, and in cardiac muscle alcohol is on the whole depressant.

6. Alcohol on the heart and circulatory system.—“Alcohol, when circulating in the blood stream, causes a gradual progressive lowering of blood pressure, with decrease in amplitude, but increase in the rate of the heart beat,” according to Brooks whose experiments were uncomplicated by the presence of anesthetics. This systemic effect is due to a series of factors involved in the circulation, namely, those which on the one hand control the action of the heart, and on the other control the size of the blood vessels, and therefore the peripheral resistance to the flow of blood. The reaction on the circulatory

system is abundantly complicated, however, by physiological factors set in action by the local stimulation by alcohol and the alcoholic liquors when taken by the mouth.

a. **The reactions of the heart.**—The heart is a complicated apparatus, physiologically consisting of the musculature of the heart, the local nervous apparatus, and the nerve centers and connections with the central nervous system. There are well defined methods in vogue in physiological and pharmacological laboratories for study-

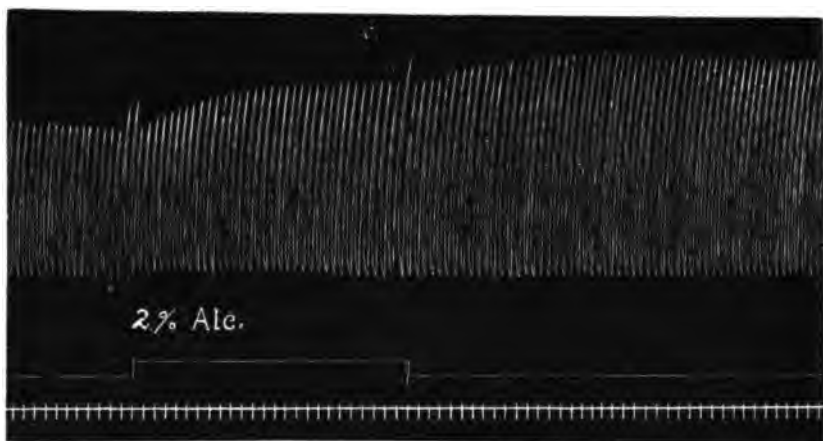


FIG. 3.—Alcohol on ventricular muscle. The strip contracts rhythmically in physiological saline 9 parts plus Ringer's solution 1 part. During the time indicated by the marker 2 per cent. alcohol in the normal solution was applied. The time record, intervals of 10 seconds. The second test was depressing. New tracing by Summers.

ing each of these portions of the cardiac apparatus. To determine the effects of alcohol on cardiac muscle two methods have been used. One method depends upon the isolation of the muscle itself, heart strips as free as possible from nervous elements, and the immersion of these strips in solutions of alcohol made up in normal or artificial physiological liquids. The other method consists in perfusing alcoholic solutions through the isolated heart or through the heart in place in the body cavity. Studies on the strips of cardiac muscle, for which the heart of the terrapin is especially favorable, show that alcohol depresses both the rate and amplitude of the muscular contractions. Stimulative effects, as indicated by accelerated rhythm, very seldom occur, in not over 10 per cent. of the experiments. These accelerations are produced by relatively strong solutions of alcohol and only at the moment of immersion. This suggests the type of local irritative effect rather than a pharmacological stimulation.

Increase in amplitude, which is so characteristic of the isolated skeletal muscle, does not often occur on isolated strips of heart muscle. The exceptional reaction is presented in Figure 3.

Perfusion of alcohol through the heart of the frog has, in the main, given confirmation of the observations from the muscle strips taken from the terrapin. The amplitude of the frog's ventricle diminishes and the rate becomes slower and often ceases, even with the weaker solutions. It is admitted by all that the stronger concentrations, 1 per cent. and over, are depressant. The auricles are even more sensitive than the ventricle. They dilate and become extremely feeble. Conduction of the auriculo-ventricular wave diminishes or is blocked.

Experiments on the isolated mammalian heart have, in the main, given essentially the same results as those listed above for the cold-blooded animals. Martin and Stevens¹ were the first to investigate the behavior of the isolated mammalian heart under the influences of alcohol added to the blood perfusing through it. Their results are indicated in the following quotation:

"When defibrinated blood containing one-half of one per cent. by volume of ethyl-alcohol is supplied to an isolated dog's heart, which has been hitherto working with uniformity, the invariable result is a very rapid and marked diminution in the work done (indicated by the quantity of the blood pumped out from the left ventricle) by the heart in a given time. When the blood contains only one-fourth of one per cent. of alcohol the result is, in most cases, the same, but sometimes is little or none. After the action of the alcohol has been fully manifested the heart can, in many cases, be restored to its original working state if supplied with defibrinated blood containing no alcohol. Blood containing but one-eighth of one per cent. of alcohol exerts no influence upon the work done by the heart, at least for several minutes."

Leo Loeb's experiments on the perfused and isolated heart showed that when alcohol was added to the perfusing fluid to the amount of 1 per cent. and more the solution became injurious to the heart. There was diminution in the rhythm and weakening of the force of the contraction. When he used solutions of 0.3 per cent. or less he sometimes found a stronger heart beat. This was particularly true if the heart was in a weakened condition. Dixon² further

¹ Martin, N. H., and Stevens, L. T., *Johns Hopkins Biol. Bull.*, Vol. II., p. 485, 1883.

² Dixon, W. E., *Jour. Physiology*, Vol. XXXV., p. 346.

elaborated this point and secured a decided improvement in the cardiac flow and rhythm by concentrations of alcohol from 0.05 to 0.3 per cent. The favorable influence on the heart action was decidedly greater when the hearts were in a weakened condition. Cushny, in his *Pharmacology and Therapeutics*, publishes a splendid instructive figure (Fig. 3), which shows the unfavorable influence of alcohol as falling more strongly on the contractile power of the auricle. This effect would markedly influence the volume and therefore the efficiency of the cardiac discharge even though the ventricle were less profoundly affected by the drug.

Isolated hearts contain local ganglia as well as muscle. But such stimulations as do occur can scarcely be claimed as specific or constant enough to be attributed to the nervous elements. Hence, whichever view one takes of the cause of the heart rhythm and sequence, the pharmacological explanation of the direct action of

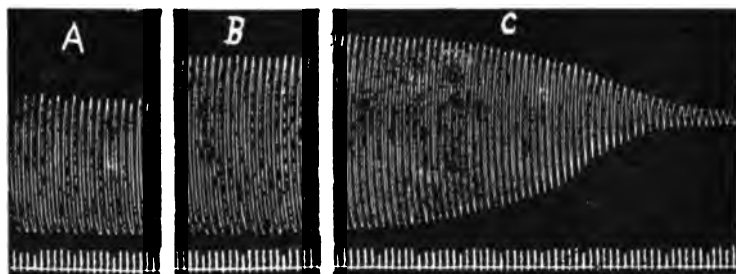


FIG. 4.—Isolated Rabbit's heart perfusing with Ringer-Locke solution. A, normal; B, after two minutes with 0.4 per cent. alcohol; C, alcohol 0.8 per cent. Time in seconds. Dixon.

alcohol on the heart is the same, namely, primary depression of function.

b. **On the cardiac centers of the medulla.**—It has been difficult to determine the direct action of the weaker doses of alcohol on the cardiac medullary centers because of the complicating reflexes. Also in an experimental procedure on mammals the medullary center is almost always rendered somewhat narcotized by the anesthetics employed. Dixon, however, has published results of experiments in which he used the beheaded dog. He injected alcohol into the carotid artery but toward the medulla. His published figures show a prompt but temporary rise of blood pressure and a change in the heart beat. A previous injection of 5 cc. of 30 per cent. alcohol in the jugular vein led to a marked fall of blood pressure. Dixon's figure presented

herewith gives his evidence for assuming that the inhibitory cardiac centers are directly stimulated by alcohol.

Brooks gave alcohol by the mouth, through a gastric fistula, and intravenously. The rise of pressure which he found on giving alcohol by the mouth he ascribes to a reflex stimulation. Brooks, by a more normal method, excludes any direct stimulative action on the medul-

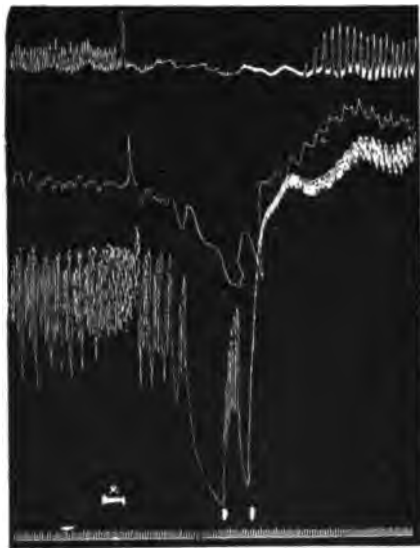


FIG. 5.—Dog, cerebrum destroyed, but medulla uninjured. The records from above downward are respiration, intestinal volume, and blood-pressure. At the mark X 10 cc. of 30 per cent. alcohol was injected into the femoral vein. The right and left vagi were cut at the marks indicated to the right. Time in seconds. Dixon.

lary center. Here again, therefore, we have the matter still in dispute and one must draw his conclusions guardedly.

c. On the peripheral blood vessels.—The arteries are under a partial tonic contraction controlled by the nerves emanating from the vasomotor centers. Under the influence of alcohol these muscles relax, thus leading to a dilatation of the blood vessels. Dixon has reinvestigated this question, showing that there is with light doses an associated vascular constriction in the viscera. This positive visceral reaction he believes to be largely central, involving an associated alcoholic stimulation of the heat regulative centers. The stronger and semitoxic concentrations tend toward a general vascular paralysis, not only in the skin but in the viscera as well.

The cutaneous dilatation is shown in the blush that comes in the

cheeks and face of those who use alcoholic liquors even very sparingly. This blushing takes place more or less throughout the whole skin and gives rise to the feeling of warmth and glow which characterizes the early effects of alcohol. Undoubtedly the sensation is one secondarily produced by the slight rise in temperature of the skin associated with the dilated blood vessels. It is this factor which makes possible the great loss of heat even in the mild stages of alcoholism. It is an oft observed fact that those who take a "bracer" of alcoholic liquors in bitter cold weather cannot resist the extreme cold nearly so well as those who refrain. The dilated cutaneous blood vessels lead to a greater loss of heat than the body can supply, hence a lowering of the body temperature.

Continued use of alcohol tends to a permanent paralysis of the cutaneous blood vessels. This paralysis is particularly striking in the cheeks and especially in the nose in chronic alcoholism. It is accompanied by degeneration of the active muscular tissue of the smaller arterioles, probably associated with decreased endothelial resistance and with fibroid thickening of the vascular walls, all of which contribute to a pathological condition of the tissues of the part.

7. **The action of alcohol on the blood.**—"Alcohol has a harmful action on the white blood cells, the agents of natural defense against infective microbes" (Metchnikoff). The corpuscles are rendered less motile and therefore are decreased in their phagocytic action. Certain microbes, especially those of erysipelas, are shown to more readily gain a foothold in the body when the phagocytes are rendered relatively inert by alcohol, and it is also shown that alcohol users are prone to suffer from this disease.

As was to be expected, the blood complements have also been shown to be distinctly reduced in users of alcohol. The importance of this change in the blood can scarcely be over-estimated in its relation to the establishment of immunity.

Neither do the red corpuscles escape injury by alcohol, due to the relative solubility of alcohol in the red corpuscle substance. As a result, large numbers of corpuscles are weakened and ultimately destroyed. The continued display of alcohol therefore has a tendency to the production of anemia.

A not unimportant secondary influence of the consumption of large quantities of the lighter alcoholic liquors is its influence on the volume of the blood. The continued absorption and disposal of large quantities of fluid tend to raise the total volume of the

blood and this reacts in the complex of the circulatory system to increase the work of the heart. The prolonged effect of this condition is great hypertrophy of that organ. Such liquors are generally associated in the long run with sufficient concentration of alcohol to produce muscular degeneration so that the beer drinker's heart becomes, not only excessively hypertrophied, but also weakened by fatty degeneration and infiltration.

8. Responses of the respiratory system to alcohol.—Alcohol affects the respiratory mechanism at two points, namely, the apparatus which controls the volume of air expired, and, second, that which controls the carrying power of the blood as regards its oxygen. Binz has given evidence indicating that alcohol slightly stimulates the respiratory centers, especially in the case of wines. Measurements have been made indicating that the total respiratory volume is increased with small doses of alcohol. Attention must again be called to the effect of alcohol on the nervous system. If one accepts the view of the depressant action of alcohol of the Schmiedeberg school, then it is obvious that this increase of respiration would take place as a secondary effect of the alcohol, either from the progressive narcosis of cerebral centers, or from reflexes arising in the mouth and stomach. In any case the acceleration of respiration is evanescent, passing quickly into a stage of depressed rate and amplitude, and the total air breathed is less. Dixon's figure shows primary respiratory depressant action, Figure 5.

The influence of alcohol on the blood whereby the total amount of hemoglobin is diminished produces a chronic diminution in the internal respiration. Such an effect would not follow after a single dose.

9. The action of alcohol on the digestive tract.—The local irritating effects of alcohol on the alimentary tract and the secondary reflexes produced thereby have already been discussed. It should be remembered that the acute secondary effects of alcohol produced through stimulation of the nervous mechanism which controls the secretion of both the salivary and the gastric glands are favorable. When alcohol has been absorbed and, through the blood, reaches these glands and their nervous mechanisms, secretory action is apparently accelerated in the gastric glands but not influenced in the salivary glands, according to Chittenden.

Alcohol mixed with the foods in the digesting stomach produces an increase in the absorbing powers of this organ. This is to be attributed to the direct effect of alcohol on the superficial epithelial

cells whereby these cells are rendered more permeable than normal.

Extensive experiments have been performed to show the action of alcohol on the digestive enzymes as such. These experiments indicate that the total efficiency of the digestive enzymes is decreased only after an alcoholic concentration of from 5 to 10 per cent. If one adds the two factors, increase in the total secretion of enzyme and the decrease in the efficiency of the enzyme present, it is obvious that the total efficiency of the digestive enzymes as such may be accelerated or weakened pretty much in proportion to the concentration of the alcohol. In therapeutic quantity and with guarded administration the medicinal balance is favorable in certain maladies.

Excessive quantities of alcohol tend to diminish the motility of the stomach and intestine, a change that is unfavorable to digestion. If the peristalses of the stomach fail to occur in the normal number and intensity then the food will be relatively stagnant in the stomach and fermentive and other changes are induced which are detrimental. This is an important factor in the development of secondary toxic substances. Where the local action of alcohol has resulted in extensive gastric ulcers both secretion and motility are interfered with, and digestion is rendered correspondingly less efficient.

10. The liver in relation to alcohol oxidations.—The physiological importance of the liver is very great, a fact that is realized when one recalls the numerous functions accomplished by this organ. The discovery of the glycogenic function of the liver by Claude Bernard in the middle of the last century gave such importance to this function as to overshadow the several no less important functions that have been explained in more recent times. Of all the complex functions of the liver one cannot overestimate the part it plays in the elimination of nitrogenous wastes. Urea and uric acid are oxidized to their final form through the agency of the liver. The other nitrogenous wastes are oxidized or their elimination facilitated through the agency of enzymes which are present in the liver. Chittenden warns in the following terms: "It is, I think, quite plain that while alcohol in moderate amounts can be burned in the body, thus serving as food in the sense that it may be a source of energy, it is quite misleading to attempt a classification or even comparison of alcohol with carbohydrates and fats, since, unlike the latter, alcohol has a most disturbing effect upon the metabolism or oxidation of the purin compounds of our daily food. Alcohol, therefore, presents a dangerous side wholly wanting in carbohydrates and fats. The latter are simply burned up to carbonic acid and water, or are transformed

into glycogen and fat, but alcohol, though more easily oxidizable, is at all times liable to obstruct, in some measure at least, the oxidative processes of the liver." The evidence indicates that the oxidation of alcohol itself takes place largely through the agency of the liver. In the presence of alcohol a relatively large amount of uric acid and a decreased quantity of urea are produced by the body.

Clinically it is a well-known fact that certain diseases of the liver are associated with chronic alcoholism. Of these one of the most common is cirrhosis. The drug not only acts on the peripheral hepatic blood vessels and parenchyma directly, but the view has been offered that the energy of the liver is consumed in the oxidation and elimination of alcohol. There is, therefore, an accumulation of nitrogenous wastes that weakens and poisons, not only the body, but the liver itself. The excessive accumulation of uric acid is offered as an explanation of the tendency to gout in alcoholics.

11. The effect of alcohol on metabolism.—The oxidation of alcohol by the body sets free its latent energy, which no doubt is utilized. However, the presence of the alcohol interferes with the metabolic processes of the body itself. In a general way it tends to depress these changes. Alcohol, when given with a fixed ration, produces a diminution in the output of nitrogen and of the total sulphur which are perhaps the best measures we have of the influence of the drug on metabolism. The variations in the specific functions of so many different mechanisms, as outlined above, all point in the same direction. The use of alcohol, therefore, as an energy producing material, is overbalanced by its toxic injuries. Even the energy which it gives is more than compensated by the weakening of the oxidizing organ, the liver.

Hunt has more recently given us an insight into the nature of the change in metabolism initiated by alcohol. He has worked with minimal and non-toxic doses fed to different species of animals through relatively long periods. He has shown, for the first time, that such temperate use of alcohol leads to marked changes in the by-products of metabolism. Proceeding on the theory that tolerance presupposes increased ability of the tissues to oxidize alcohol, he established his point by tests with methyl cyanide which on oxidation liberates toxic substances. In his tests a mouse which recovered from a dose of 0.5 mg. of methyl cyanide per gram of weight, after a month's feeding with small quantities of alcohol in the food, quickly succumbed to a dose of 0.2 mg. Furthermore, Hunt found that the ethereal sulphates were relatively strongly increased, 3 to 50 per cent.,

under alcohol feeding, indicating failure of complete oxidations. This discovery, together with Edsall's observation of unoxidized phenol in the urine of chronic alcoholics, may also be explained as indicating injury to liver metabolism under alcohol.

12. **The elimination of alcohol.**—Alcohol is practically all oxidized in the body as shown by the calorimetric determinations of Atwater, except when excessive quantities are introduced. Of the remaining alcohol a trace only is eliminated by the lungs as shown by Cushny, and the remainder is excreted through the kidney.

The excretion of alcohol by the kidney, especially when excessive amounts are taken, leads to certain cumulative effects which produce irritation. This produces a tendency to nephritis, which interferes with the normal functions of that organ.

13. **The effects of repeated use of alcohol on tolerance, and on the germ-plasm and fertility.**—Alcohol, like a number of the alkaloids, when used repeatedly leads to the production in the tissues of a degree of tolerance. The body protoplasm acquires an increased power of oxidation and becomes less responsive to the drug. This accounts for the ability of a chronic user to consume such large quantities of alcohol without intoxication. Unfortunately these protoplasmic changes are associated with an unconquerable desire for the alcohol. The nervous tissue gets into such a state that the will power is no longer able to withstand the craving, and the individual consumes an excessive amount of alcohol. The moral and ethical side of this question is emphasized in voluminous literature.

One of the most important changes produced in the body by alcohol is that on the germ-plasm. Both man and animals show a great decrease, not only in fertility, but in the number of normal offspring. Hodge has bred dogs from alcoholic parents in comparison with normal dogs and finds that the alcoholics show an average fertility of one-half, namely, 50 per cent. Of the young produced by normal parents an average of 90.2 per cent. were normal young. In alcoholic dogs this percentage of normal offspring is reduced to 17.4 per cent. Hodge quotes an instance of a study made on human parents showing that the number of viable children from alcoholic parents was 17 per cent. as against 88.5 per cent. from normal parents. The alcoholic families of both man and dogs produce a high percentage of defective and deformed offspring, many of the young in fact being born dead. The strength and development of the human embryo are dependent upon two factors, inheritance from the germ-plasms and nutrition during embryonic life. That alcohol influences the inheritance factor,

through the father as well as through the mother, is indicated by the number of deformed and defective children born of parents of which one alone is alcoholic. Of the children born many are non-viable, that is, for one reason or another they are unable to take nourishment and do not develop normally. Possibly these defects are due to failure of full development of some internal structure.

14. **The alcohol habit and disease.**—Physicians, as well as laymen, now take into account the habit-forming tendency produced by alcohol. With its repeated use the tissues not only acquire power to oxidize and dispose of the alcohol, but there results a change which leads to a craving that cannot be satisfied. It is this factor which often leads to a rapid disintegration of an otherwise apparently strong and healthy individual. Through its effects on the defensive qualities of the blood, i.e., the phagocytes and the anti-toxins produced by them, as well as because of the general changes in the efficiency of the circulatory apparatus, the profound changes in the metabolism of the liver, the tissues in general are rendered non-resistant to the invasion of disease. Germs which otherwise would be successfully combated and eliminated from the body are able to gain a foothold. This factor was especially emphasized by the observations of Hodge on alcoholic dogs. An invasion of disease into his experimental kennels resulted in the death of several of his alcoholic dogs, whereas the normals recovered after relatively light attacks. Similar observations have been made at the various clinics on men. In quite recent years it has become a well-established fact that the excessive users of so mild an alcoholic drink as the Munich beer, are rendered more liable to disease and show a higher death rate.

IV.

Condensed Summary of the Effects of Alcohol on the Human Organism.

Alcohol is a local irritant, acting on the skin of the mouth and on the mucosa of the stomach. It produces secondary reflex effects when so applied, some of which are quite favorable. When introduced into the general system, alcohol produces a narcotic effect, especially on the nervous tissues. It diminishes the activity of the cortex in its most complex relations, as shown by decrease in intellectual power, emotional control, and will power. The lower centers of the central nervous axis are temporarily released from the inhibitive

control of the cerebral cortex, but later are depressed in function and ultimately paralyzed. Alcohol diminishes the efficiency of the vital organs, like the heart, blood vessels, the blood, and their nervous mechanisms, in certain cases with an initial but evanescent stimulation. In acute use it favors the reflex increase of the digestive secretions, but with a decrease in the amount of enzyme present in a given quantity of secretion. It also diminishes the digestive efficiency of the enzyme. Alcohol produces irritation and ulceration of the stomach after prolonged use, especially in the concentrated form. It also diminishes the motility of the stomach and the intestine. It interferes with the metabolism of the body, especially with the oxidations in the liver of the by-products of protein and nuclear metabolism. It tends to produce local inflammation in the kidney. It leads to the formation of the alcohol habit, and, in prolonged and chronic use, changes the germ-plasm and thereby diminishes both fertility and the viability of offspring. It breaks down the resistance of the body to disease by destroying the efficiency of the phagocytes, and leads to premature death of the individual.

THE ANESTHETICS.

CHAPTER III.

ETHER

I.

Historical.

Members of the group of anesthetics are characterized by the physical property of volatility, also by the physiological property of producing unconsciousness, and therefore loss of pain without any great danger to life. They have proven an invaluable boon to suffering humanity in their use in surgical anesthesia. The anesthetic properties of ethyl ether were introduced to the public by the activities of Morton in Boston in 1846. Chloroform was introduced the next year, 1847, by Simpson at Edinburgh. Nitrous oxide soon after came into popular use for periods of short anesthesia. In determining priority it appears that the anesthetic action of both nitrous oxide and of ether had previously been discovered, and had been used in isolated cases; but for one reason or another this knowledge had not become public property. Jackson demonstrated the anesthetic power of ether in 1841, and Long first used ether in surgery in 1842. But the honor of introducing ether into public use really belongs to Morton, not as its discoverer, but by virtue of his success in the public demonstration of its surgical value.

It is now well known that even the ancients produced a degree of anesthesia or insensibility to pain in surgical operations. They used alcohol, some plant infusions, and in some cases a degree of asphyxiation, thus securing carbon dioxide anesthesia. But the introduction of drugs as a regular routine in relieving pain in surgical operations dates from the popular demonstration of ether in Boston by Morton in 1846.

The anesthetics, by virtue of their great volatility and ready absorption by the tissues, are peculiarly adapted to surgical purposes. Inhaled, they come into intimate contact with a relatively large absorbing surface, the pulmonary capillaries. They quickly pass into the blood and are as quickly distributed throughout the body.

On the other hand, their elimination is by the lungs, a process which is at first equally rapid and efficient. Volatility with ready absorption and elimination gives an immediate and advantageous control of the degree of narcosis quite impossible with non-volatile drugs that must be introduced by the slow process of gastric and hypodermic absorption, and eliminated by the even more retarded paths of general excretion.

The relative action and safety of ether and chloroform have aroused a great amount of investigation throughout the surgical world. In Europe chloroform gained the greater favor, and has been used most extensively down to comparatively recent years. In America ether has been in greater favor and, at the present time, is used almost exclusively, except where it is contraindicated in special surgical cases. It is difficult to determine the relative danger of the two and our statistics depend almost entirely on figures derived from hospitals where conditions are most safe for its successful administration. Statistics from St. Bartholomew's from the years 1875 to 1890 show a death list for:

Chloroform.	in 18,526 cases,	13 deaths,	1 death to	1,502
Ether in 8,491	" 3	" 1	" " 2,830
Gas and ether	in 12,941	" 1 death,	1	" " 12,941

In the cases collected by Julhard, the death-rate was:

Chloroform 1 to	3,258 for 524,507 cases
Ether 1 to	14,987 for 314,738 cases.

The above figures indicate that the chloroform is about five times more fatal than ether, but that neither is especially dangerous. The cases do not, however, take into account the toxic influence on the organs produced by the anesthetic, such as develop secondary changes that may lead to death at some later period. Chloroform is generally recognized as much more dangerous from this latter point of view.

II.

Outline of the General Action of Ether.

1. **Stages of anesthetic effects.**—Since ether and chloroform are used primarily for the production of anesthesia, it will be desirable to present at once the successive general stages recognized in the process of anesthetizing. These stages have been described by numerous

writers, and somewhat variously classified. However, four phases of action may be recognized as described in the changes in the general functions of the whole body. These are:

1. The excitement stage,
2. The intermediate stage,
3. The surgical anesthesia stage,
4. The toxic stage.

The *excitement* stage is characterized by the presence of profound reflexes which are induced by the action of the ether on the mucous membranes of the respiratory tract. These lead to irregularities and some acceleration of the respiration, and often to violent coughing. Respiration may occasionally be completely inhibited for several seconds, even producing considerable cyanosis. These periods are followed by deep and spasmodic respiration in which deep draughts of relatively saturated ether vapor are drawn into the lungs. There is reflex irregularity of heartbeat with considerable quickening of the pulse. There is a tendency to emotional states coupled with mental incoördination. In the late stages of this period analgesia is produced.

The *intermediate* stage is usually short, but is associated with mental delirium, often strong muscular contractions or even spasms. There is great irregularity of respiration characterized by deep inspiratory gasps. The cutaneous blood vessels are dilated, and narcosis and unconsciousness quickly supervene.

The stage of *surgical anesthesia* is characterized by complete loss of pain sensations, complete relaxation of the voluntary muscles, and loss of general muscular reflexes. The breathing becomes regular as in a deep sleep, the pulse is regular, somewhat rapid, and the blood pressure medium. The light reflexes are lost and the pupil widely dilated. The corneal reflexes are present in light anesthesia, dropping out in the deep stages, a valuable indication of the degree of anesthesia. The temperature of the body is lowered, due to the greater dilation of the cutaneous blood vessels and to lowered metabolism. The anatomic mechanisms are still intact and respond to reflexes in the usual way, except in the very deep and profound anesthesia.

The *toxic* stage or danger stage is indicated by a marked slowing followed by complete cessation of respiration. The blood pressure becomes low with paralysis of the vasomotor center, the heartbeat is weak from direct muscular anesthesia. The respiratory center often entirely ceases; even when the blood-pressure is relatively high, the heart will continue beating for some seconds. In mammals the circulation is kept up until the blood becomes strongly cyanotic, at which stage

there usually occurs a series of respiratory gasps in response to the direct effects of the highly venous blood on the respiratory centers.

TABULATION OF THE CHARACTERISTICS OF THE STAGES OF ANESTHESIA.

1. Excitement stage	<ul style="list-style-type: none"> coughing respiration accelerated pulse quickened vertigo occasional sharp reflex cardiac inhibition emotional tendency incoordination dilated pupil analgesia
2. Intermediate stage	<ul style="list-style-type: none"> delirium muscular spasms respiratory irregularity dilated blood-vessels narcosis unconsciousness
3. Surgical anesthesia stage	<ul style="list-style-type: none"> pain sensations lost muscular relaxation with loss of muscular reflexes regular breathing regular pulse with medium blood-pressure light reflexes lost, pupil widely dilated corneal reflexes present in lighter stages absent in deeper temperature lowered by greater loss of heat alimentary reflexes present except in deepest stage
4. Toxic stage	<ul style="list-style-type: none"> respiratory center becomes slower and ceases blood-pressure very low with paralysis of the vaso-motor center heart weak from direct muscular anesthesia

III.

The Details of the Action of Ether.

1. The action of ether on the central nervous system.—The changes in the function of the central nervous system are the ones most important to surgical anesthesia, and many of the details have already been given in the summary above. From this list it is obvious that the narcosis is a descending one. It begins with the suppression of function of the higher or cortical centers, and is closed with the loss of function of the great vital centers in the medulla. There is an evident similarity of action to that produced by alcohol, also to that produced by chloroform as will appear later.

Ether narcosis is preceded by a short stage of stimulation or accelerated function. Waller has demonstrated this point by a direct

study of nerve fibers. He determined the volume of the nerve impulse as measured by the action current which was given in response to a constant stimulus. This he found to be sharply increased at the initial stage of the action of ether. If this principle were accepted in general it would account for a number of phenomena noted in the stimulation stage in anesthetizing. However, many of the phenomena can also be accounted for largely on the basis of descending nerve narcosis, the principle considered in the study of alcohol.

Many of the effects, when ether is first inhaled, are produced, not by the action of the ether on the central nervous system, but by



FIG. 6.—Ether vapor on nerve irritability. A muscle nerve preparation is so arranged as to subject the nerve only to ether vapor, which was applied between the arrows. Electrical stimulation at 10 second intervals. The first two contractions of the muscle are normal. The successive five contractions during the application of ether vapor. Slow recovery occurs on the removal of the vapor by a stream of fresh moist air through the apparatus. New tracing by Wallace.

reflexes started by the local irritant action on the mucous membrane of the mouth, nasal cavity, and respiratory tract. Some anesthetists avoid this action in hypersensitive individuals by a preliminary narcotic, by cocaine sprayed into the upper portion of the respiratory channel, or by nitrous oxide gas.

In the deeper stages of anesthesia, sensory stimuli no longer arouse the more complex centers of the central nervous system. Certain centers in the spinal cord, and especially in the medulla, are still capable of executing reflexes. Experiments of Bernstein indicate that local anesthesia of the spinal cord produces a block for sensory nerve impulses for spinal nerves of the anesthetized region, whereas reflexes still occur through the anesthetized region upon stimulation of sensory nerves of a non-anesthetized region. This indicates that the block to reflex nerve impulses occurs primarily in some of the sensory connecting links, rather than in the motor cells of the cord and brain stem. In the deeper anesthesia the motor cells also lose their irritability.

The nerve centers in the medulla respond to reflex stimulation long after the cerebral cortex is narcotized, and after sensory reflexes

through the cord are lost. In animal experimentation the stimulation of the various sensory nerves, as, for instance, the sensory fibers of the vagus, produces, not only respiratory effects through the medullary center, but cardiac and vasomotor effects through their respective centers located in the same region.

The retention of reflex irritability under ether anesthesia is of great surgical importance. It permits reflex stimulations during operations that may be, and generally are, important factors in producing the undesirable condition of shock. In recent practice certain accessory drugs, i.e., urea, quinine, or novocain, are being used to block the course of sensory nerve impulses, thus eliminating the undesirable reflexes.

2. **The action on the respiratory center.**—In the excitement and intermediate stages the respiratory center undergoes great change, chiefly due to secondary stimulations developed by local peripheral irritation. In the toxic stage these cells are directly affected and are markedly depressed, respiration ultimately ceasing from loss of function of the cells of the respiratory center. Recovery of the irritability of the respiratory center in ether paralysis is always possible so long as there is a considerable amount of blood-pressure, a factor that has been emphasized by Dixon. This is one of the chief points in favor of ether versus chloroform. Anesthesia so deep as to suspend the function of the respiratory center rarely causes a fall of blood-pressure of more than 50 or 60 per cent., usually much less. Artificial respiration will, therefore, generally recover the case.

3. **The action of ether on the circulatory system and on blood-pressure.**—The blood-pressure is maintained at a rather high level during ether anesthesia. Just at the beginning of the action of ether the blood-pressure rises slightly, i.e., during the stimulation stage, a change that is chiefly secondary in character. Occasionally there may be a reflex fall of pressure, see the heart action discussed below. In surgical anesthesia the blood-pressure is slightly below normal, though generally strong and effective. At death from ether the pressure falls slowly until the respiratory center ceases, then it usually drops rapidly to 20 to 30 per cent. of the normal. The early general pressure fall is followed by a secondary or asphyxial rise of variable amount, then a final sharp fall to approximately zero.

4. **The action of ether on the heart.**—Ether produces changes in the heartbeat both by direct action on the heart muscle and through the nervous mechanism. The first effects on the heart are reflexes which arise from the irritant stimulation of portions of the

respiratory tract. Occasionally there will be a complete inhibition of the heart following the first two or three whiffs of ether. This usually lasts for only a moment, after which the heart resumes its beating with the usual vigor. In the intermediate stage, as the ether is distributed through the system, there is generally a slight acceleration of the heartbeat from direct muscular stimulation. In the late toxic stages the heart ceases to beat also from direct muscular action. These facts can be beautifully illustrated by the laboratory methods for studying the isolated heart. The perfused frog's heart almost always shows an appreciable acceleration in rate when a

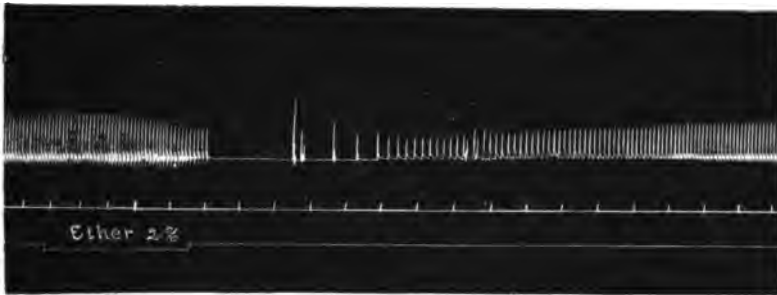


FIG. 7.—The action of ether on the isolated heart of the dog when perfused through the coronary arteries, 2 per cent. by volume in Ringer-blood solution. The composition of the Ringer's solution was NaCl 0.9 per cent. + KCl 0.042 per cent. + CaCl_2 0.026 per cent. Time in 5 second intervals. New tracing by Kruse, Boutwell, and Heldt.

weak ether solution is used. If the solution is made stronger then the acceleration is followed by a marked slowing, often by complete stopping. With still stronger solutions slowing and stopping occur at once. With slowing of the frog's heart there is a decrease in the amplitude of the contractions and a dilation of the heart chambers. Undoubtedly these are direct muscular effects. Isolated strips of turtle's heart muscle exhibit similar phenomena, the ventricle becoming slower and weaker, and the sinus also losing its waves of tonic contraction. The isolated mammalian heart also shows a characteristic picture of anesthesia, as does the heart studied in the complex of the body. Leo Loeb studied the effect of ether on the isolated mammalian heart, showing that 0.4 per cent. ether in solution in the blood leads to a stoppage of the rhythm.

5. Ether on the blood vessels.—In the stimulation stage of ether

anesthesia there is a marked flushing of the skin, an effect that is a secondary reflex response to the local sensory stimulation of the respiratory tract. However, this stage is quickly followed by the direct systemic action of the ether on the blood vessel walls and on the vasomotor center of the medulla. The latter is lowered in its sensitiveness to the usual medullary reflexes, thus leading to a loss of vascular tone. The decrease in peripheral resistance to the blood

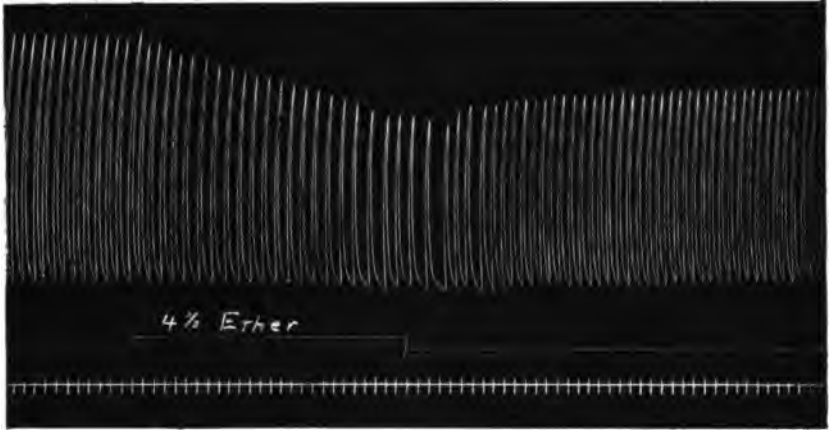


FIG. 8.—Ether, 4 per cent. solution in physiological saline, on the isolated cardiac muscle of the terrapin. Time, 5 seconds. New tracing by Summers.

flow results in most of the fall of blood-pressure noted under ether. The vasomotor center, fortunately, does not completely lose its reflex irritability, in fact this irritability is only slightly diminished to the great mass of autonomic reflex stimulations.

The peripheral vascular actions of ether are not uniform throughout the whole body. Along with the marked flushing of the skin, Kemp has shown that in the dog the blood vessels of the kidney are constricted. Of course such a constriction leads to an interference with the secretion of urine, and may produce complete anuria. It is possible that this renal action is due to the direct local action of the ether during excretion. The kidney is an important organ in the elimination of ether, especially during surgical anesthesia, when the concentration in the blood is greatest. The local concentration during excretion leads to local irritation and therefore inflammation, mild nephritis, or in prolonged anesthesia marked nephritis will result, a condition that is later associated with albuminuria, which is its characteristic symptom.

6. **Action of ether on voluntary muscle.**—It is easy to demonstrate by laboratory experiments that voluntary muscle is anesthetized as well as is nerve. If a muscle-nerve preparation be suspended in a moist chamber and the nerve alone be surrounded by ether vapor, the nerve shows a decreased irritability as judged by the response of the muscle to maximal and minimal stimuli. If the muscle alone be subjected to ether vapor it also shows a decrease in irritability lasting for some moments after the ether vapor is replaced by pure air. Ether narcosis of the nerve is preceded by a brief and slight increase in irritability, a fact which has not been shown for muscle.

7. **Action of ether on the alimentary canal.**—The effects of ether on the alimentary tract are also twofold, namely, systemic and local irritant with its corresponding reflex changes in function. In ordinary procedure the most marked stimulations occur in the mouth and upper respiratory tract, the reflex effects of which have already been discussed in relation to respiration and circulation. Important alimentary reflexes are produced through the various secreting glands connected therewith. The salivary glands, for instance, are markedly stimulated and a marked increase in the secretion of saliva follows. The smaller glands of the mouth and of the walls of the bronchial tubes also have their secretions increased. The movements of the alimentary canal are depressed by ether, especially in the deeper stages where they may be stopped altogether. But "Ether can be given sufficient to prevent any movements of skeletal muscle without interfering with the alimentary canal" (Cannon).

Meltzer has recently called attention to the possibilities of anesthetizing per rectum. While ether is absorbed in this locality it is not considered a very favorable method of anesthetizing, owing to the high local irritant action of the anesthetic. No specific effects of ether on the efficiency of the alimentary tract as a digesting mechanism have thus far been shown.

8. **The absorption, distribution, and excretion of ether.**—Overton and Meyer have advanced theories accounting for the absorption of ether and chloroform. Their view is that the anesthetics produce their characteristic action by virtue of great solubility in the cell lipoids. The fats and fatty compounds of the cells dissolve the ether and this changes the physical-chemical constants of the cell protoplasm, thereby interfering with its normal function. Such tissues as the nerve cells, which have a high content of lecithins, etc., would by this theory receive a greater quantity of ether than other tissues, as for example, the skeletal muscles. This theory furnishes a good working

hypothesis, though there is considerable evidence against its complete acceptance.

In any case the ether markedly interferes with the metabolism of the cell protoplasm. Heat production is diminished and nitrogenous metabolism also. That the protoplasmic structure is to some extent disorganized is shown by the degenerative changes, fatty infiltrations, etc., which follow deep anesthesia. The kidney, the heart, the nerves, all have been shown to undergo varying degrees of fatty degeneration following surgical anesthesia. This is evidence of the degeneration of protoplasm, and of the fact that the drug is toxic in a chemical sense as well as in a physical.

Ether is primarily eliminated by the same channel by which it enters the body, namely, the respiratory tract. Its great volatility favors its elimination from the body by this channel. Complete elimination takes place only very slowly, and ether can be detected in the breath for many hours after only a mild inhalation. Elimination also takes place through the kidney where ether is excreted with the urine. The slow passage of the urine along the tubules favors irritant action of ether on the renal cells, thus producing inflammation and fatty degeneration, i.e., nephritis.

IV.

Condensed Summary of the Action of Ether on the Body.

Ether is a most reliable surgical anesthetic. It produces complete loss of consciousness, is relatively free from danger, and permits of rapid recovery when the drug is eliminated. The stages of anesthesia are (1) an excitement stage characterized by accelerated respiration and heartbeat, slight rise of blood-pressure, a local irritation of the respiratory tract with reflex dilatation of the pupil, a confusion of mental impressions. This stage is followed by (2) an intermediate one in which there is mental incoördination, a tendency to muscular reflexes that are uncoördinated in character, irregularity of respiration, analgesia, and finally complete unconsciousness, passing over into the third stage of surgical anesthesia. This is characterized by complete muscular relaxation, insensibility to pain, loss of muscular reflexes, regular respiration and heartbeat, an even blood pressure, loss of eye reflexes in the deep stages, but retention of the function of the medullary center. The final or toxic action of the drug is characterized by slow respiration with final stoppage, slight fall of blood-

pressure with slow and weak heart, which continues to beat for some moments after respiration ceases and before final death. Ether produces the most profound effects on the nervous system, but practically all the other tissues are anesthetized. The heart is reflexly inhibited, but finally slowed and paralyzed by direct action. The glandular tissues are reflexly stimulated to secretion, especially the salivary glands and the glands of the respiratory tract, with later depression. The kidney is directly and locally irritated, with a tendency to vascular constriction and suppression of urine, followed in the after period by albuminuria. Local actions in the lungs are irritation with a slight predisposition to inflammatory processes. Fatty degeneration may follow as a sequence in the liver, the kidney, and the heart. On the whole, ether is relatively safe, about four to five times safer than chloroform.

CHAPTER IV.

CHLOROFORM

I.

Details of the Action of Chloroform.

1. Stages of anesthetic effects.—With chloroform, as with ether there are well-marked stages of effect during the production of anesthesia. These stages are characterized by very definite symptoms which are similar in character to those produced by ether. Chloroform is much more toxic than ether and must be administered with its vapor well diluted with air. On this account the excitement stage and also the intermediate stages as described for ether are very much foreshortened with chloroform.

It is generally stated that the local effects of chloroform are less irritant than in the case of ether. However, this difference does not preclude the local stimulations of the mucous membrane of the respiratory tract and the production, therefore, of all the local reflexes described for ether. These, it will be remembered, are interference with the respiratory rate and depth often with a temporary complete inhibition of respiration, increased reflex secretion of saliva, and marked irregularity of the circulation due primarily to reflex cardiac inhibition. A few deep whiffs of concentrated chloroform vapor at the beginning of its inhalation often lead to complete but temporary inhibition of respiration.

In surgical anesthesia the greater intensity of action of chloroform is still operative, therefore there is a much narrower margin between the light and the deep stages, and between the anesthesia and the toxic stage. It is evident that slight variations in the proportion of chloroform vapor and of air will produce relatively great variations in the degree and intensity of anesthesia. In short, it requires a greater degree of skill on the part of the anesthetist to maintain a uniform and safe chloroform anesthesia. The percentage of saturation of chloroform vapor in the inspired air has been investigated by Rosenfeld.¹ His results on rabbits are given in part in the following table:—

¹ Rosenfeld, Max, *Archiv für Pathologie und Pharmakologie*, Vol XXXVII., p. 52, 1896.

The Rapidity of Onset and Degree of Chloroform Anesthesia in Rabbits in Relation to the Percentage of Concentration of Chloroform in the Air.

Exp. No.	Per cent. by volume of chloroform vapor	Time before complete anesthesia, and notes.	
6	0.54—0.69	No anesthesia in 1 hr. 43 min.	Reflexes present, Heart rate depressed.
5	0.93—1.01	Anesthesia in 40 min.	Respiration regular for 4 hrs.
4	0.93—1.01	" " 53 "	Heart rate accelerated.
3	1.16—1.22	" " 31 "	Respiratory failure in 1 hr. 56 min.
2	1.41—1.47	" " 36 "	Heart markedly depressed.
			Respiratory failure in 1 hr. 13 min.
1	1.63—1.65	" " 11 "	Respiratory failure in 45 min.

2. The action of chloroform on the central nervous system.—

With chloroform as with ether the narcosis of the nervous system is in a descending direction. The higher cortical functions pass through a very slight and brief stimulation stage, followed by a complete, but temporary loss of function. The suspension of function involves, first the cerebral cortex and the great tracts of the sensory and the association centers, later the spinal reflexes, and finally the great vital centers of the medulla. Many of the early effects produced by chloroform are accomplished through variations in the reflexes of different portions of the nervous system.

Reflexes that have their origin in primary stimulation of sensory surfaces of the respiratory tract can, to some extent, be depressed by previous treatment that lowers the sensibility of the cutaneous nerve endings, as for example by cocaine spraying or previous application of other drugs with local depressant action.

Of the reflex effects the most profound are those which react through the respiratory center and through the cardiac inhibitory center. Some animals, as for example the rabbit, are especially sensitive in this regard. A whiff of chloroform vapor is often sufficient to inhibit respiration in the rabbit for many seconds. Occasional clinical experiences of the anesthetist show that a certain percentage of individuals of the human species also respond more completely to these local stimulations. In the later stages of chloroform anesthesia, the vital centers which are involved in the early reflex responses are narcotized by the direct action of the chloroform on the nerve cells. If the narcosis be deep then the sensitiveness of the centers to the usual sensory stimuli is lowered and the responses are correspondingly diminished.

The danger stage of anesthesia depends chiefly on paralysis of the respiratory center. As a rule the irritability of the respiratory center can readily be recovered if the anesthetic has not produced too great

a fall of blood-pressure. However, chloroform has a profound effect upon blood-pressure, and, unfortunately, tends to a marked lowering of pressure at a time somewhat preceding the paralysis of the respiratory center. On this account, deep chloroform anesthesia is much more dangerous than that with ether. Artificial respiration

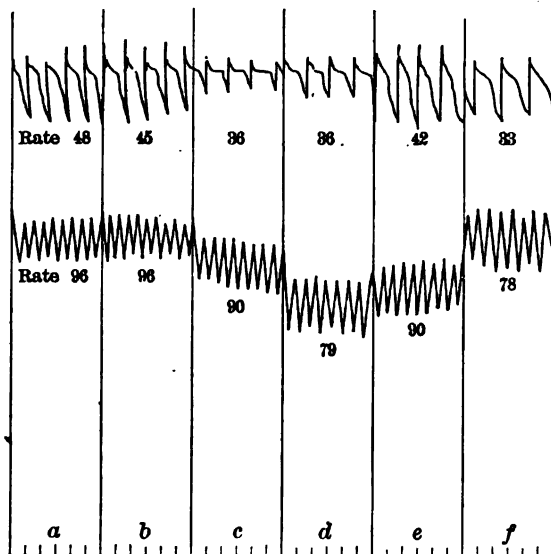


FIG. 9.—The mild influence of chloroform on blood-pressure, heart rate, and on respiration. The respiratory and cardiac rates are indicated on the tracing. Between the successive portions indicated from *a* to *f* there have been omitted 10, 10, 15, 40, and 100 seconds, respectively. New tracing by Gullion.

will often suffice to recover activity of the respiratory center when its function has been lost by a temporary toxic stage. This recovery is, however, much more difficult to attain than in the case of ether.

3. The action of chloroform on the circulatory system,—blood-pressure.—Chloroform tends to lower blood-pressure. In mammalian experimentation one rarely notices any initial rise of blood-pressure. The fall of pressure is accompanied, perhaps caused by an initial reflex slowing of the heart. Deep anesthesia is accompanied by narcosis of the musculature, not only of the heart, but of the arterial system as well. During surgical anesthesia the blood-pressure is considerably below that of the normal. If the anesthetic is pushed far, then there will be a marked and sudden fall of blood-pressure, with a slow and weak heartbeat and ultimate death. In mammals, as a rule, the respiratory center ceases its action before paralysis of the

heart is complete. This, however, depends upon the rapidity with which the chloroform is given.

4. **The action of chloroform on the heart.**—The first effect of chloroform on the heart is a reflex slowing produced by the local irritation of the sensory nerves of the mouth and naso-pharyngeal region. This slowing usually passes away after the anesthetic induces its systemic effects. During the initial systemic action there is a brief

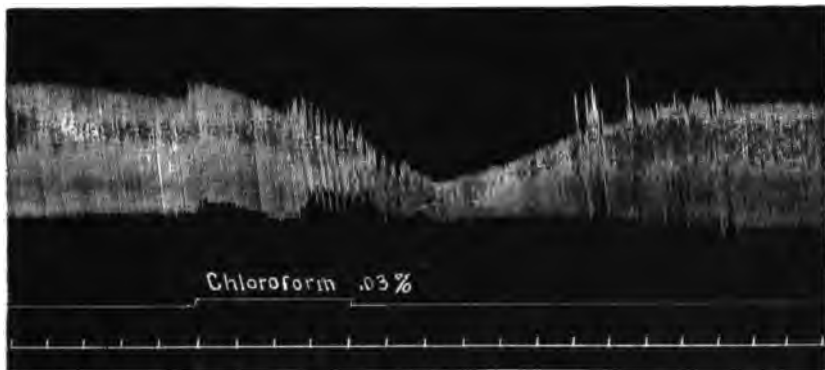


FIG. 10.—The influence of chloroform on the contractions of the isolated heart of the cat. The chloroform was in Ringer-blood solution, 0.03 per cent. by volume. There is some lag before the chloroform solution reaches the heart tissue, also a slight mechanical displacement at the time the solution was turned on. Time, in 5 second intervals. Perfusion as marked. New tracing by Boutwell, Heldt, and Kruse.

period of slight irregularity of the heart accompanied by periods of accelerated rate.

Chloroform has a marked depressing action upon the functions of the heart muscle. In deep anesthesia this depression accounts in large measure for the slow and weak pulse. Rhythmic beating strips of heart muscle cut from the ventricle of the terrapin respond very delicately to chloroform anesthesia. The amplitude is quickly diminished and the rate rapidly slowed and inhibited after sufficient vapor is used. If the anesthetic reaches the stage of complete inhibition of rate then the rhythm is restored only after a long latent period. Chloroform and ether are usually in sharper contrast in this respect than shown in Figures 8 and 11.

The mammalian heart is also very susceptible to chloroform vapor, presumably on account of the muscular effects of the drug. Isolated mammalian hearts show a diminution in rate and a great decrease in the amplitude when weak solutions of chloroform are added to the perfusing liquid. When simultaneous cardiograms are made from

the auricle and from the ventricle of an experimental mammal these effects on the rhythm and amplitude are shown in fine contrast. Cushny, and Gottlieb and Meyer, have published figures on this point. Cushny, especially, has demonstrated a more marked influence on the excursions of the auricle than on the ventricle. Ventricular contractions will be medium strong and vigorous at a time when the auricular contractions are reduced to a minimum.

The more profound stages of chloroform suspension of function of

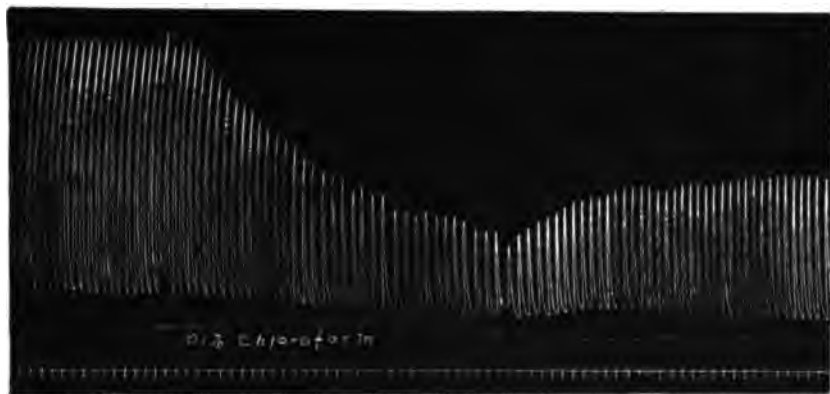


FIG. 11.—Chloroform 0.1 per cent. in physiological saline on the rhythm of the ventricular muscle of the terrapin. The marked decrease in amplitude and rate is characteristic. This strength of chloroform will often completely inhibit the rate within five to ten seconds. Compare with Fig. 8 showing the effect of ether. Time in 5 seconds. New tracing by Summers.

the cardiac muscle do not immediately destroy the vitality of the tissue. The function can be reëstablished, though with much greater difficulty than with ether. However, a pronounced toxic effect upon the protoplasm follows after such deep stages. A certain proportion of the heart protoplasm is killed, as indicated by the fatty degenerations which follow after a lapse of two or three days. These degenerations are in fact of great vital importance, hence very deep chloroform narcosis is to be avoided under all circumstances.

5. Action of chloroform on the blood-vessels. Following the first few inhalations of chloroform vapor there is a reflex vasodilation shown by the flushing of the skin. This stage is quickly followed by a direct systemic action of the drug on both the vasomotor center and the blood-vessel walls. The vasomotor center loses its delicacy of response to the usual stimulations, thus allowing a

passive dilation of the blood-vessels. The smooth muscles of the blood-vessel walls are directly narcotized. This leads to relaxation and dilation and to a corresponding fall of blood-pressure.

Local organs are affected by the dilation of the peripheral blood-vessels and the fall of blood-pressure. The kidney, for example, is markedly affected. The dilation of the renal vessels immediately allows greater carrying volume of blood, though this is more than counterbalanced by the general fall of blood-pressure. The general result is that the solution of chloroform vapor in the blood is brought into contact with the renal tissue in relatively greater amount, i.e., the slow speed of the blood through the vessels allows of proportionately greater time for local absorption, hence the renal tissue is correspondingly deeply anesthetized. This is shown, in part, through the partial suspension of function of the kidney. In a word, the somewhat more sluggish stream of blood through the kidney is, not only in itself unfavorable to the excretion of urine, but is favorable to the production of anesthesia of the renal tissue, still further reducing the power of excretion. As chloroform is excreted by the renal tubules it follows that there will be a somewhat concentrated action of the drug at this point.

Other organs, such as the liver, are similarly affected. Doubtless this is the explanation of the tendency to fatty degeneration in the kidney, liver, etc., following prolonged or deep chloroform anesthesia.

6. Action of chloroform on the voluntary muscles.—Voluntary muscles are directly anesthetized by chloroform. This is readily shown by the decrease in irritability of the muscles to direct stimulation during anesthesia. When isolated skeletal muscle is anesthetized with chloroform to the point of complete loss of irritability it can be recovered only by complete removal of the vapor and after prolonged treatment with air or oxygen. The anesthesia stage for skeletal muscle is deeper and more profound for chloroform than for ether.

7. The action of chloroform on the alimentary canal.—Chloroform will anesthetize the tissues of the alimentary tract as it does every other tissue thus far examined. These effects are, as in ether, both indirect through the reflexes and direct. The direct effects come only after the chloroform is absorbed into the blood and has passed through the circulation. This stage is characterized by a depression of function, i.e., by anesthesia of the muscles of the stomach and intestine and by a suspension of the secretion of the digestive glands.

The reflex effects are accomplished chiefly through the local action of chloroform on the naso-pharyngeal and mouth regions. These

reflexes last only a brief time and consist in the increase in the secretion of the saliva and probably of gastric juice. The normal peristalses of the stomach and of the intestine are suppressed by chloroform, though the matter has not been sufficiently investigated for full statements.

8. The absorption of chloroform.—The great volatility of chloroform favors its administration admixed with air by way of the respiration. Though it has a relatively low solubility in water and in the watery content of the cells, i.e., a saturation factor of one part in two hundred, 0.5 per cent., still this is well above the efficient concentration for anesthetic purposes. Its solubility in the cell lipoids also favors its absorption by the tissues. Probably, as Meyer and Overton have indicated, this lipid solubility is a factor in the distribution and relative intensity of action of chloroform on the tissue. This would account for its specific effects on the nervous tissue, the red blood cells, etc. Roaf gives good evidence to show that the reactions of chloroform in the body are not entirely physical.

Metabolism is lowered by chloroform. This is evident from the great diminution of the output of nitrogen as well as the lowering of functional activities which characterize chloroform anesthesia. Chloroform tends to destroy the protoplasmic organization; this undoubtedly is the contributing factor which leads to more or less fatty degeneration after its administration. If the destruction of the tissue is slight, then ultimate repair occurs and no untoward effects follow. If the injury is marked, then fatty degeneration occurs with its chain of pathological disarrangements from which death will occasionally follow. Unfortunately these delayed effects are not always charged up to the primary cause, i.e., chloroform anesthesia.

9. The excretion of chloroform.—Chloroform, like ether, is eliminated from the body by the respiratory tract and by the kidney. The respiratory tissue through which the chloroform vapor enters and in a large measure leaves, and the kidney are relatively deeply anesthetized. They, therefore, feel the evil effects of the anesthetic as expressed in degenerative changes.

II.

Condensed Summary of the Action of Chloroform on the Body.

Chloroform is a widely used surgical anesthetic, comparing in value with ether. It produces complete loss of consciousness and a descend-

ing elimination of function of the great divisions of the central nervous system. Rapid elimination and recovery follow when the drug is removed. The stages of anesthesia are the same as with ether, except that the excitement stage and the intermediate stage are passed over more quickly. Chloroform vapor must be administered with great dilution in air. Slight variations in the concentration of the vapor produce more profound variations in the degree of anesthesia. Chloroform is several times more toxic than ether, therefore, more dangerous. In the danger stage there is complete loss of muscular reflexes, great weakness of the respiratory activity, slow and weak heart, dilated blood-vessels, and correspondingly low blood-pressure. The toxic stage is marked by a cessation of respiration through direct action on the respiratory center and a quick fall of blood-pressure and weak heart. Recovery of the toxic depression of the respiratory center is rendered very difficult because of the associated low blood-pressure. The heart is directly anesthetized, greatly slowed, and finally paralyzed. The alimentary tract is at first reflexly stimulated though slightly, and later depressed because of the direct action of the drug on the smooth muscle. The kidney parenchyma is directly anesthetized, and, to some extent, undergoes toxic degeneration following chloroform anesthesia. The nervous tissue responds in a similar manner. Fatty degeneration of the kidney, of the liver, and of the heart muscle characterizes the after-effects of prolonged chloroform narcosis. Chloroform is many times more intense in its action, therefore more dangerous than ether.

CHAPTER V.

NITROUS OXIDE.

I.

Historical and General.

The anesthetic action of nitrous oxide, N_2O , was discovered at the end of the eighteenth century. It is therefore the oldest of the anesthetics unless one give consideration to the use of alcohol along this line. The action of nitrous oxide was first noted by Davy. Like many other valuable observations this one was not followed up, hence the peculiar value of this agency was not utilized until after the introduction of ether and chloroform. Wells in 1844 rediscovered the action of nitrous oxide, though again this act did not result in its immediate introduction into general use.

Nitrous oxide produces anesthesia, but only when administered in concentrated form. This fact has led to considerable discussion of the nature of nitrous oxide action. It is claimed by some that the gas does not produce anesthesia, but instead does produce a degree of asphyxiation by the exclusion of oxygen. However, experiments by Kemp and others have shown that the nitrous oxide has a direct effect upon the nervous tissue. Kemp experimented on dogs, allowing them to breathe nitrous oxide mixed with oxygen in known concentrations. He found that when an animal was anesthetized with nitrous oxide mixture and then allowed to breathe a mixture of nitrogen and oxygen in the same proportions, it quickly recovered from the anesthetized condition. Kemp analyzed the gaseous content of the blood and thereby proved that there was sufficient oxygen present to maintain life, provided an indifferent diluting gas only was present. These experiments indicate that asphyxiation cannot account for the anesthetic effects and that nitrous oxide is a true anesthetic.

II.

The Action of Nitrous Oxide on the General Activities of the Body.

If nitrous oxide is inhaled in concentrated form for a few minutes, it quickly produces a degree of intoxication followed by unconscious-

ness. The early symptoms are not unlike those of alcoholic intoxication except that a leading characteristic is that of uncontrolled laughter. It is this that has led to the name "laughing gas." There is a marked lowering of response to sensory stimuli and a decrease in the acuteness of pain sensations. This condition is characterized by a lack of coördination of the voluntary muscles and a lowering of the sensibility of the central nervous system in general. This stage is followed by complete unconsciousness in which respiration is weak and in which there is a tendency to dyspnea. The circulation continues even though there be temporary stoppage of respiration. If the gas is removed, unconsciousness lasts only a brief period, 40 to 60 seconds. Recovery is almost instantaneous, and the individual suffers no untoward after-effects.

The maintenance of prolonged anesthesia with nitrous oxide is difficult, owing to the high concentration of the gas required. However, for brief operations, the nitrous oxide has proven a valuable anesthetic to be recommended, because of the ease of application and because of the lack of danger in its use. Practically no instances of death have been recorded which are attributable directly to the anesthetic. Its freedom from danger makes it invaluable for such operations as the extraction of teeth or for minor surgical operations, but its use has been largely restricted to dental work.

This gas has no characteristic special actions in the body. Such symptoms as occur other than general anesthesia can be largely attributed to the disturbance of the respiratory balance. Partial anesthesia produces in the body secondary physiological effects as detailed in the discussion of the reactions from ether and chloroform.

Nitrous oxide responses show a large percentage of disturbance of this type. There is, therefore, a marked rise of blood-pressure, increase of the heart rate, disturbances of the respiration rate, etc.

III.

The Administration of Nitrous Oxide.

The surgical administration of nitrous oxide is best accomplished with a controlled admixture of gas with pure oxygen. This mixture is secured by a mechanical apparatus, of which there are several devices in use in various institutions. With such an apparatus as that invented by Hewitt it is possible to administer nitrous oxide of any concentration. His apparatus contains three chambers, nitrous oxide

in one, pure oxygen in one, and from these cylinders mixtures can be made in any proportion in the third chamber. A close fitting face mask is connected by means of a wide tube with the chamber containing the mixed gas, from which inhalations take place. However, the later forms of apparatus have a rubber bag attached to the mask



FIG. 12.—Application of Hewitt's nitrous oxide and oxygen apparatus in surgical operation. After Hewitt.

(which is preferable), or to a side tube on the connecting tube. The inhalation of external air is controlled through a side valve.

In practice it is best to fit the mask and then allow the patient to breathe pure air until everything is tested. The gas bag is then filled with pure gas and this is breathed for from 10 to 15 breaths, a quantity usually sufficient to put the patient thoroughly asleep without inducing cyanosis. The gas bag is then refilled with oxygen

and gas in the proportion of 1 to 6 or 8.¹ Great variation exists in the individual requirements as to the percentage of gas and oxygen. In starting the anesthesia with pure gas, great care must be taken not to allow cyanosis, and if such appears during the anesthesia, the

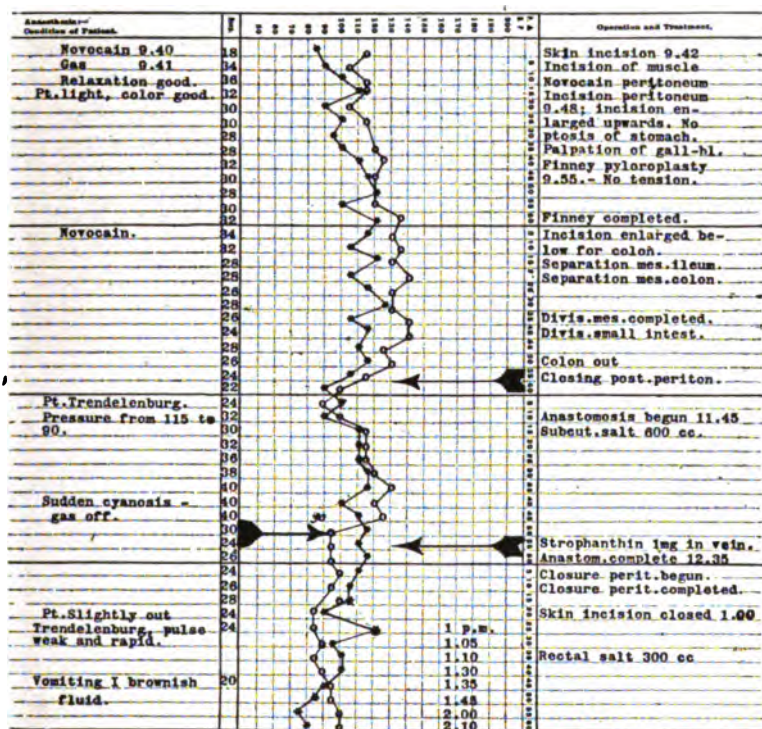


FIG. 13.—Chart showing nitrous oxide anesthesia associated with local infiltration of 1 to 400 parts novocain. The chart shows the changes in blood-pressure and pulse rate during a three-hour operation for the resection of the right half of the colon. Bloodgood.

practice is to allow the patient to have one or two breaths of pure air, thus tending to keep the blood-pressure under uniform control.

When nitrous oxide is the only general anesthetic used, then a local analgesic is applied at the point of incision or wherever intense nerve stimulation may occur. For this purpose use novocain in 1 to 400 parts.²

¹ For details given in this place I am indebted to several papers by Dr. J. C. Bloodgood, and to personal information from Dr. J. E. Stowers, who has assisted Dr. Bloodgood in numerous operations.

² Bloodgood, J. C.: *Annals of Surgery*, Vol. LVIII., p. 721, 1913.

An illustration of the practical use of nitrous oxide gas by this method is given in the preceding chart, Figure 13.

Nitrous oxide is being more and more used as a preliminary anesthetic to chloroform or ether. It has the effect of producing a quick partial anesthesia, thus enabling the patient to pass more safely and comfortably over the excitement stage of ether and chloroform. This procedure has also the economic value of reducing the quantity of ether required. There is practically no danger from the administration of nitrous oxide for brief anesthesia. Yet the disturbances of the circulation induced by the temporary degree of asphyxiation are associated with some little danger in atheroma, or in certain types of cardiac irregularity in which nitrous oxide is to be excluded.

CHAPTER VI.

CHLORAL HYDRATE.

I.

Historical and Chemical.

In 1868 Liebrich described chloral hydrate as a new hypnotic, since which time it has become a reliable and widely used drug for that purpose. Chloral hydrate is a representative of the methane series, with the structural formula:



The discovery of the physiological effects of this drug has led to the examination of numerous other representatives of the series, and has given us a group of drugs with general narcotic powers. In general they are characterized by a change in function more nearly resembling that in sleep and hence known as hypnotic. Chloral hydrate is far less volatile than either chloroform or ether. However, it is very soluble in the body fluids, hence can be absorbed readily from the alimentary tract. There is a numerous series of representatives of the hypnotic group, but none have become of primary importance. Of this series may be mentioned chiefly chloral hydrate, urethan, veronal, and sulfonal.

II.

Outline of Pharmacological Effects of Chloral Hydrate.

1. *It produces a narcosis resembling deep sleep.*
2. *The narcosis is characterized by a lowering of sensibility to stimulation with diminution of pain.*
3. *There is a marked lowering of blood-pressure with slowing of the heart rate and a tendency to a diastolic pause.*

III.

Details of Pharmacological Action.

1. **The general symptoms.**—The general symptom complex produced by chloral hydrate is remarkably like that of natural sleep in a profoundly fatigued individual. There is at first inertia, drowsiness, with sluggishness in response to severe stimulation. This stage passes into a sleep-like stage of unconsciousness. The sensory mechanisms remain irritable and the patient reacts to strong stimuli which may still arouse in him consciousness, unless the amount of chloral administered be excessive. 1 to 1.5 grams produces drowsiness with sleep, while a dose of 4 to 5 grams produces a profound degree of unconsciousness from which it is very difficult to arouse the patient, even with excessively vigorous stimulation. Since chloral greatly lowers the stimulation threshold, pain sensations are diminished. Recovery from chloral is relatively slow, 4 to 5 hours after a gram dose, 10 to 12 hours after a 5-gram dose.

It is for these general symptoms that the members of the group have their special value, namely, as depressants of the central nervous activity.

2. **Chloral hydrate on the nervous system.**—The general symptoms described above are in fact nervous system effects. Chloral hydrate seems to specifically depress the functional activity of nerve cell groups in the central nervous system. Of these groups those cells in the cerebral cortex are of the most profound importance since the depression of their sensibilities leads to diminished responses to the usual inflow of sensory impulses. The influence, however, is more profound in that the coördinative activities of the neurons in the cortex are depressed.

Such responses as result in the basic nuclei of the nervous system from chemical or possibly hormone reactions are proven to be lowered. Of these nuclei those located in the medulla are the most important. For example, the respiratory center in the medulla has recently been shown by Cushny¹ to be lowered in its sensibility to carbon dioxide stimulation. It is true that this center is still responsive to afferent nerve stimulation while under the influence of chloral hydrate. The change in the nerve cells produced by chloral hydrate comes on only slowly and under the influence of a rather strong dosage. Rabbits make little response up to a dose of

¹ Cushny, A. R.: *Journal of Pharmacology and Experimental Therapeutics*, Vol. IV., p. 380.

0.17 gram per kilo given intravenously. When the dosage reaches 0.28 gram there is a distinct fall of respiratory rate, and after 0.4 gram a sudden fall in the rate together with an increase in the depth of respiration accompanied by forced breathing. Under this condition of mild chloralization, i.e., 0.17 grams per kilo, "the reflex movements and general activity are very much diminished and the carbon dioxide production must fall in corresponding measure." "As the dose is increased the excitability of the nerve center is so far reduced that it can no longer maintain the rate even under the double stimulus of carbon dioxide and anemia, but it continues to deepen. Finally its rate is reduced to one-ninth of the normal, while its depth is doubled." Chloral hydrate narcosis does not, however, lower the rate of oxidations of sea urchin eggs.

CHAPTER VII.

MORPHINE AND THE OPIUM SERIES.

I.

Historical and Chemical.

The dried juice of the poppy, *Papaver somniferum*, contains a series of some twenty alkaloids of which morphine is present in greatest amount. The juice or milk is obtained by scarring the unripe seed pods. The exudate is evaporated in the open air, and the dried product is known as opium. Opium is produced in largest amount in the Asiatic countries. Turkey, Persia, East India, and China, and also Egypt are the great producers of opium. In recent years an increased quantity has been grown in Europe, and its cultivation is now being introduced into the United States. The medicinal reactions of opium have been known since ancient time. The alkaloid morphine is of special interest as being the first alkaloid chemically isolated in pure form, 1804.

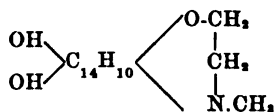
Of the series of alkaloids present in opium, the following are the most important:

Morphine	$C_{17}H_{19}NO_3$
Codeine	$C_{18}H_{21}NO_3$
Papaverine	$C_{20}H_{21}NO_4$
Narcotine	$C_{22}H_{25}NO_7$
Thebaine	$C_{19}H_{21}NO_3$

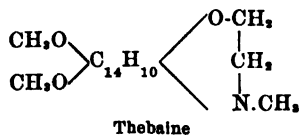
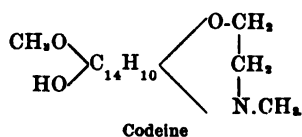
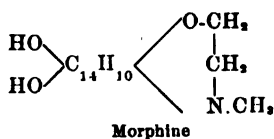
The percentage of the different alkaloids present in opium varies extremely, depending upon the country and climate, and upon the method of gathering and drying. Opium contains from 10 to 20 per cent. of morphine, the former being the average requirement of the medicinal drug. Opium on the market, however, may contain from 3 to 18 per cent. of morphine, 1 to 10 per cent. of narcotine, 1 to 2 per cent. of codeine with traces of the large number of alkaloids that have been isolated from this mixture.

The chemical relationships of the opium alkaloids is complex.

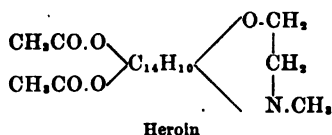
The structural formula of morphine, for example, is still in question. It is apparently a derivative from a hydrated phenanthrene nucleus, and has been given by Knorr as follows:



Codeine and thebaine differ from morphine in that the hydrogen of the hydroxyls is substituted by methyl, one methyl in the former, two in the latter alkaloid. With this substitution the change in the physiological action approaches that of the caffeine group, where an increase of methyl in the series produces the same type of physiological change in the action. The chemical relationships may be expressed by the following formulæ:



In modern synthetic chemistry a series of products have been built up by substituting radicals for one or more of the hydrogen atoms in morphine. Of these heroin is of chief importance from the pharmacological and therapeutic point of view. Heroin is a diacetyl morphine of the following formula:



Morphine as an alkaloid is very insoluble in water, while its salts are quite soluble, six per cent. or more. The salts have the same pharmacological action, and are generally used, the sulphate being official.

II.

Outline of Pharmacological Action of Morphine and the Opium Series.

1. *Morphine produces a marked depression of the central nervous system in the descending direction preceded by slight initial stimulation. The change of greatest importance is the great decrease of the perception of pain.*
2. *Depression of the blood-pressure with marked cardiac depression after larger doses.*
3. *An initial increase followed by marked decrease of the peristalses of the alimentary canal associated with pyloric stricture.*
4. *A constriction of the pupil from central action, with dilation in the paralytic stage.*

III.

Details of Pharmacological Action.

1. **The central nervous system.**—The action of morphine on the central nervous system varies greatly. In animals there is a marked variation in response by the different species, especially among the mammals. In man the general picture is one of slight initial increase of function followed by very marked depression.

The first and primary effect on man of a mild dose of morphine, and especially of opium, is a gradual diminution in the activity and control of the higher psychic centers. There is a marked decrease in the power of attention, followed by a dreamy, sleepy, imaginative state which is the condition desired by the opium abuser. This stage is characterized by lack of power of consecutive thought, a diminution of acuteness of judgment, and inability to long maintain effort if it involve logical sequence. The picture evidently indicates a selective action on the association centers and other higher psychic centers of the cerebral cortex. There is a certain degree of excitement sometimes shown in the so-called imaginative stage somewhat similar to that produced by certain alcohols, especially absinthe. However, morphine is much more sedative and does not lead to the excessive muscular activities produced under the former drug. Morphine greatly reduces the power of self-control, therefore leaves the individual in the position of a reflex animal.

In the incipient stages of morphine intoxication there is a delay

in the facility with which intellectual acts are accomplished. This is quickly followed by a languid state in which the individual is aroused only by much more vigorous stimuli than are usually required. He may pass into a dreamy, sleepy state in which the sensations of pain are greatly blunted. The usual reflexes from stimulation of the skin are very greatly decreased though not eliminated. The change

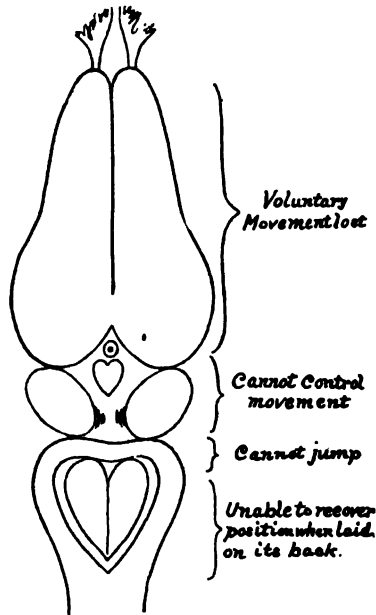


FIG. 14.—Dorsal view of the frog's brain. The legend shows the progressive effect of morphine and other narcotics which destroy the higher functions of the brain in the descending direction, i.e., in the reverse order of their racial development. Dixon.

depends upon the central depression rather than any direct effect upon the peripheral sensory apparatus. The chief value of morphine as a medicinal agent depends upon this characteristic reduction of the sensitiveness of the central nervous system to pain stimulation. In fact, morphine is probably the best known and most valuable alleviator of pain in the whole category of drugs.

With excessive doses of morphine the person lapses into a deep sleep from which he is awakened only with extreme difficulty, and even then only into a semi-conscious state. However, even in the advanced toxic stage, i.e., until respiratory paralysis is approaching, he can be aroused sufficiently to move around. Power of voluntary movement is only lost in the final toxic stage. In this deeply toxic

the functional influence of the nervous complex, and secondarily through the direct action of the drug on the cardiac muscle. The heart rate is reduced to half or even less of its normal rate with a characteristic large and swinging amplitude, when a small to medium dose of morphine is given an otherwise undrugged animal. This effect comes from a primary and sharp stimulation of the inhibitory center in the medulla. If, in a mammal, the vagus nerves are sectioned before morphine is injected, the heart rate instead of slowing is markedly accelerated, a fact which may be interpreted as a direct stimulation of the accelerator center, see Figure 17. In this latter case there is still a great fall in the blood-pressure which is indicative of a general vascular dilation, an effect that can be explained by either of two conceptions, namely, vasodilator stimulation or vasoconstrictor paralysis. In light of the positive evidence as regards the cardiac centers one is inclined to consider the phenomenon a positive vasodilation.

With the stronger intoxication from morphine these stimulative reactions on the medullary vascular centers pass into depression, i.e., narcosis.

Morphine directly influences the rhythm, the contractility, and probably the conductivity of cardiac muscle. The rhythm is more profoundly depressed, though the amplitude may be, and generally is greatly diminished. Isolated portions of cardiac muscle, when bathed by relatively strong solutions of morphine may have the rhythm completely obliterated. This influence is of the nature of a narcosis and can be slowly removed by eliminating the contact of the drug. Undoubtedly this direct influence of morphine on heart muscle is a factor in the complex of the symptoms with all stronger doses of morphine, but does not appear in the reaction to therapeutic concentrations.

Recently Eyster and Meek¹ have shown that the intravenous and subcutaneous administration of morphine to dogs not only slows the heart, but produces characteristic irregularities in the cardiac action. Intravenous injections of 30 to 60 milligrams of morphine usually slightly increase the pulse for a few minutes, then there comes on a marked slowing of the rhythm. Still later there develops arrhythmia in which there may be a sino-auricular block or an auriculo-ventricular block. "Electrocardiographic records indicate that the slowing and arrhythmia are due to disturbance of conduction between the point of origin of the cardiac impulse and the auricle, and between

¹ Eyster and Meek, *Heart*, Vol. IV., p. 62.

the auricle and ventricle." At any time during the irregularity of the heart rhythm the administration of atropine completely recovers the regular rhythm. This antagonism of atropine for the morphine effect leads the authors to conclude that the peripheral cardiac change is a vagus effect. This view has been strengthened by the known fact that vagus stimulation may lead to similar blocks of cardiac conduction.

EFFECT OF MORPHINE ON THE ELECTROCARDIOGRAM (EYSTER AND MEEK)

Exp.	Normal						After Morphine					
	P	Q	R	S	T	RT	P	Q	R	S	T	RT
6	8	6	25	6	-7	0.192	1.5	2	19	6	+6	0.227
7	8	14	27	0	-5	0.240	2	8	28	0	-1	0.280
8	2	9	38	6	+2	0.207	1	6	30	6	+2	0.235
9	8	8	30	6	-4	0.185	0.5	6	24	5	+3	0.235
10	2	6	25	6	-2	0.243	1	2	19	6	+3	0.262

4. A review of the normal movements of the stomach and intestine.—The stomach is divided into the two great cavities, the

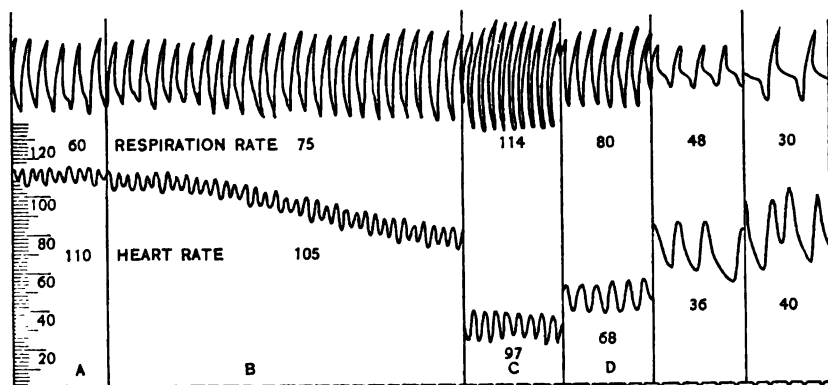


FIG. 16.—Intravenous injection of 2 cc. of 1 per cent. morphine on blood-pressure and respiration. Vagi intact, dog. The respiratory rates and heart rates as shown. Time in seconds.

A, 10 seconds before morphine.
B, 30 seconds after morphine.
C, after 2 minutes.

D, after 4 1-2 minutes.
E, after 7 minutes.
F, after 28 minutes.

fundus and the pylorus. These cavities are bounded by muscular bands, the cardiac sphincter, between the esophagus and the stomach, and the pyloric sphincter at the boundary between the pylorus and

utes after food enters the stomach there is set up a series of regular peristaltic contraction waves, beginning at first in the zone intermediate between the cardiac and pyloric regions and progressing in orderly sequence toward the pyloric end of the division. These waves originate successively nearer the cardiac orifice until they ultimately involve the whole stomach. The waves progress over the stomach at a remarkably uniform rate—in the cat, where Cannon first described them, one wave in ten seconds, requiring about twenty seconds for its

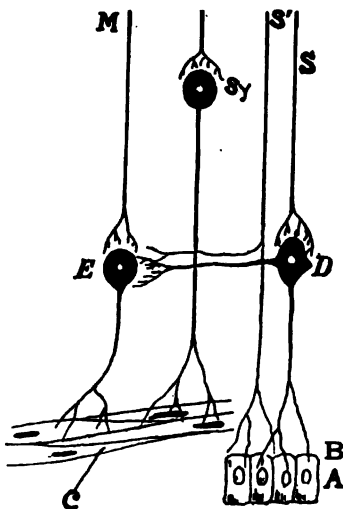


FIG. 19.—Diagrammatic representation of the scheme of innervation of the alimentary canal. *A*, mucosa; *B*, sensory nerve endings; *C*, gastric or intestinal wall; *D* and *E*, sensory and motor cell bodies in the enteric plexus; *M*, motor neurons, vagus fibers for the stomach and upper portion of the intestine, sympathetic fiber lower down; *S* and *S'*, afferent sensory nerves; *Sy*, sympathetic ganglion, pre-postganglionic synapse, inhibitory path for the mammalian canal. The fiber *S'* is introduced to Dixon's original figure on the basis of his foot-note. Modified from Dixon.

completion. In man the waves continue during digestion or until the stomach is completely empty, six to eight and more hours. The peristalses control, therefore, two factors; first, by their pressure over the food mass they produce a gentle kneading of the gastric juice into the food, and second, after the surface of the food is eroded off by the digestive process the waves of muscular contraction carry it forward toward the pylorus, which periodically relaxes, permitting discharge into the duodenum. Each discharge of acid food into the duodenum leads to a reflex closure of the muscular sphincter, hence the mechanism insures an even and regular feeding of the intestine from the great reservoir, the stomach.

Two sets of nerves control the muscular movements of the stomach; first, the sympathetic nerves which reach the stomach by way of the splanchnics, and are inhibitory in character, and second, the vagus nerve, which is motor in character. The elaborate nerve plexuses of Auerbach and of Meissner form a local enteral nerve mechanism that is not yet fully understood. The indications are that the sympathetic nerve fibers run through these plexuses to end on the muscles, while the vagus fibers form synapses in these plexuses. That the stomach possesses sensory nerve endings can no longer be questioned (Pawlow). These endings are involved in the production of the secondary gastric secretions, through stimulation by the products of digestion which result in reflexes terminating in the gastric glands. There is some evidence that the sensory mechanism may produce local reflexes through local ganglia in the walls of the organ.

The intestine also possesses circular and longitudinal muscle coats, but the only valve-like arrangement is that between the ilium and the colon, the cecal valve. The two types of muscular contraction occur, one a progressive peristalsis, which, under certain conditions, may become reversed, anti-peristaltic, and second, alternate contractions and relaxations of adjacent portions of the circular musculature, described as segmentations by Cannon. The segmentations intimately mix and knead the intestinal content, while the peristaltic waves periodically drive the content along the tube. The nervous mechanism regulating the muscular movements is similar to that just described for the stomach, i.e., there are motor fibers, inhibitory fibers, and local ganglia.

5. The action of morphine on the stomach and on the intestine.—It is obvious that the alimentary tract may be influenced by morphine through the action of the drug at any one of the following series of points:

1. The motor centers in the medulla.
2. The inhibitory centers in the medulla.
3. The pre-ganglionic ends in the peripheral ganglia of the vagus path.
4. The pre-ganglionic endings of the inhibitory path.
5. The motor endings of the vagus post-ganglionic neuron.
6. The inhibitory endings of the splanchnic ganglionic neuron.
7. The muscle tissue directly.
8. The local sensory apparatus.

There is great variation in the effect of morphine on the alimentary tract of animals of different species. In man the initial effect

is to produce a degree of nausea with the accompanying reflex increase in the secretions of the glands and sometimes vomiting. This nausea is not produced until absorption is accomplished and is undoubtedly through the agency of the vomiting centers of the medulla. In dogs and in the lower mammals vomiting almost invariably occurs, but in man only a mild degree of nausea is the rule. The nausea is limited to the earlier stages in morphine narcosis. It may reappear in the recovery stages following deep narcosis. That the nausea is not due to any peripheral action is indicated by the fact that it comes on

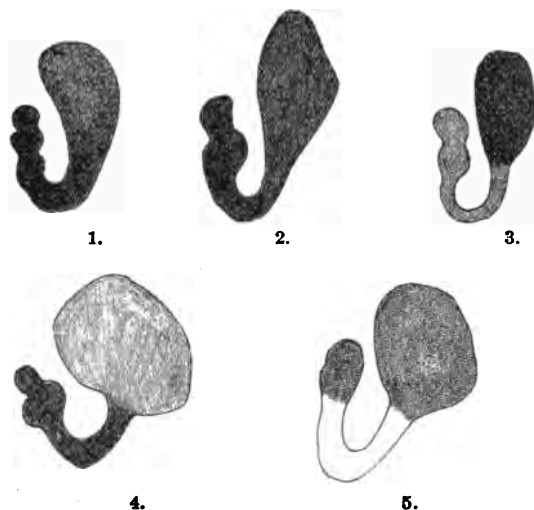


FIG. 20.—Morphine 30 milligrams given subcutaneously to a cat. Röntgen-ray photographs of the stomach after a meal of potatoes, containing bismuth subnitrate. 1, normal stomach uniformly filled, showing pyloric peristalsis; 2, 32 minutes after morphine, showing general contraction of the stomach wall, pyloric peristalsis; 3, one hour after morphine, strong contractions of middle region of the stomach, pyloric peristalsis; 4, after 3 hours, fundus widely dilated, middle segment contracted, pyloric peristalsis; 5, after 6 hours, middle region of the stomach strongly contracted, separating the fundus from the pylorus. After Magnus.

whether the drug be given by way of the mouth or by the hypodermic needle.

The effect on the movements of the stomach is slight at first, usually producing in man only a mild increase in peristalsis. In dogs with duodenal fistula it has been observed that morphine greatly delays discharge of the content of the stomach. Magnus, using the Roentgen ray method of Cannon on cats and dogs, found that under the influence of morphine the food remained stagnated in the fundic end of the stomach, due to cramp contractions of the cardiac-pyloric region. And although peristaltic waves traveled over the pyloric

antrum, the pyloric valve, too, remained closed. Since this contraction cramp persisted for several hours the discharge of the fundic content was markedly delayed, 7 to 24 hours, instead of occurring in the normal 3 hours. It is evident that morphine will produce the same general failure in emptying of the stomach as that occurring in various pathological conditions, such as atonia. Though the mechanism affected is different, a stagnation of the food takes place in each case together with fermentation and decomposition. How morphine brings on an increased contraction of the sphincters has not been adequately explained. One can but draw the inference that this effect is primarily central and is similar to that which produces an inhibition of the heart through the vagus mechanism.

Morphine also influences the peristalses of the intestine. A relatively small dose increases peristalses, but the stronger doses tend to depress apparently by lowering the irritability and contractility of the muscle walls. These facts have been brought out by comparative studies on mammals. In some animals, especially the dog, the intestinal contractions are sharply increased at the beginning of the influence of morphine. The dog exhibits, not only nausea and vomiting, but purging as well. Even in man, occasional individuals will be found showing this greater sensitiveness to morphine. These effects in the early stages of morphinization are undoubtedly due to central stimulation of the vagus-motor fibers for the intestine, and of the centers probably spinal, controlling the lower part of the alimentary canal, the colon and rectum. In the later stages, the symptoms are due to paralysis of the nerve endings.

However, in man morphine and opium have long held a reputation for producing constipation. Magnus' work, previously quoted, gives one clew to the explanation of this effect on the intestine. Another factor has been cleared up by Pohl. Pohl studied the motor mechanism of the intestine after bilateral section of the splanchnics, i.e., the inhibitory paths. In normal animals this operation is accompanied by an increase in the sensitiveness of the responses of the canal to vagus stimulation, a sensitiveness that lasts several hours. If at any time after splanchnic section, morphine be given there is a marked decrease, in fact practical disappearance, of vagus control over the intestine. Notwithstanding this elimination of vagus endings there is an increase in peristaltic activity. This observation of Pohl, together with that of Magnus on the stomach, would seem to receive explanation in the action of the morphine on the local neuro-muscular mechanism. The exact point of action is somewhat a matter of inference, and one

is naturally influenced by his physiological conception of the origin of alimentary peristalses.

6. **Morphine on the eye.**—Morphine produces a characteristic contraction of the pupil of the eye. Up to the extremely toxic stage the pupil is contracted down to a pin point, which is one of the diagnostic symptoms in morphine poisoning. The explanation of this action is also in dispute, since it might result either from paralysis of the dilator mechanism or from stimulation of the constrictor. The

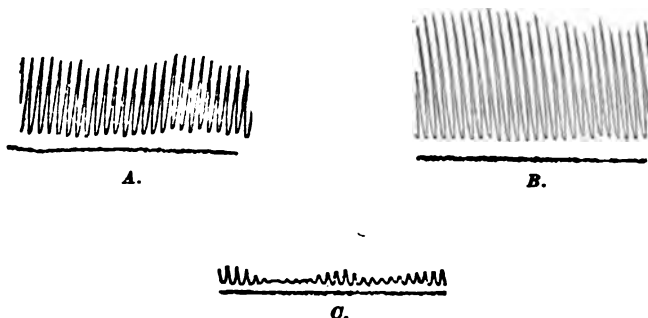


FIG. 21.—Action of morphine on the isolated loop of the small intestine, suspended in Ringer's solution. Rabbit. A, normal movement; B, stimulating effect of 0.042 per cent. morphine hydronitrate; C, paralyzing effect of 0.142 per cent. of morphine. From Magnus.

constrictor mechanism is, indeed, the probable cause of the constriction, not by a stimulus of the center as one might suppose, but rather by a morphine narcosis of some central mechanism normally acting as an inhibitor of this center, thus setting free the normal tone of the center. That it is not local is proven by the non-effect of the drug in local applications.

7. **Morphine on the Frog.**—The frog is a simple animal for the study of the effect of morphine, because of its lesser complication of nerve structure. The simple brain of the frog can be removed part by part, and the physiological effects of such removal are well known. Morphine given to the frog diminishes the activities of the animal, suspending the functions of the brain in a descending series in a way closely comparable to the type of change noted when the parts of the brain are removed by operation. After a toxic dose for a frog has been acting for several hours, from six to twenty-four, the spinal cord begins to show a marked increase in sensitiveness to reflex stimulation. A slight stimulus may lead to regular muscular spasms not unlike those produced by strychnine. In the ordinary acute effect of the drug this stage is not observed on

the frog, but in the cat it is often approached early, due to the extraordinary sensitiveness of the cord and brain-stem of this animal to morphine. Interest in this strychnine-like effect is brought out by a comparison with other members of the morphine series. These produce increasing stimulation in the order in which the drugs are named on page 66. Thebaine, for example, produces a change in the central nervous system closely comparable to strychnine itself. In the cat morphine produces a thebaine-like type of poisoning.

8. Morphine on metabolism.—Morphine decreases metabolism. This is shown by measuring the amount of nitrogen eliminated during morphinization. Various observers have shown that the total amount of nitrogen eliminated during morphine narcosis is very markedly diminished. Along with the decreased metabolism is generally noted a decrease in body temperature. The fall of blood-pressure and dilation of the cutaneous blood-vessels lead to a greater heat loss. This, without the necessary increase in heat production, a normal response to lowered temperature that is reduced if not suppressed under morphine, leads to a fall in the average body temperature.

Morphine produces some specific changes in the body metabolism, as for example, in the glycogenic function of the liver. Under its influence the sugars are eliminated from the body in greater quantity, for a certain degree of glycosuria generally follows the giving of morphine clinically.

IV.

Action of Codeine, Papaverine, Thebaine, and Heroin.

The alkaloid, *codeine*, produces effects similar to morphine. The chief difference is in the relative increase in the various stimulative phases and a decrease in the depressions noted under morphine. Codeine produces a distinct narcosis, but the sleep is not so pronounced as that produced by morphine. A greater degree of excitation follows the use of larger doses. It is also claimed that codeine more markedly stimulates the vascular nervous mechanism, leading to a greater fall of blood-pressure with greater dilation of peripheral blood-vessels than occurs with morphine.

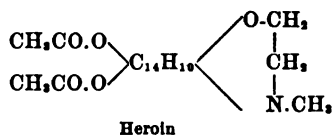
Codeine does not produce so great a depression of the respiratory center and is therefore to be preferred to morphine, especially with children. Codeine is only about one-twentieth as toxic as morphine, a variation that rests largely on its decrease in toxic influence over the respiratory center.

Papaverine has a narcotic influence very similar to that of codeine.

Narcotine has a more specific influence on the spinal cord and its action resembles thebaine, though it is not so toxic.

Thebaine, in comparison with the other members of the morphine series, possesses far less narcotic and more stimulating powers. Thebaine on animals often produces mild muscular spasms very similar in character to those following a mild dose of strychnine. In the cold-blooded animals, frogs and turtles, this strychnine-like action is an early symptom, while the similar action of morphine comes on only after many hours and following a deep narcotic stage. Reference to the chemical formula shows that thebaine contains two methyl groups in substitution for hydrogens of the two hydroxyls in the morphine. This substitution is undoubtedly the cause of the diminished narcotic and the increased stimulating effect of the thebaine.

Heroin. Of the synthetic or artificial alkaloids derived from members of the morphine group, heroin may be especially mentioned.



The two acetyl substitutions produce in heroin a desirable sedative, acting mildly on the respiratory apparatus and on the pain mechanisms. Heroin is not considered so toxic as morphine.

V.

The Excretion of the Morphine Group.

Morphine is partly oxidized, but also excreted from the body unchanged. A hypodermic injection of morphine is eliminated by excretion through the glands of the alimentary tract, and the mucous membrane of the stomach and intestine. Faust¹ shows that 70 per cent. can be recovered from the feces of a non-immunized animal. A certain proportion of the morphine is temporarily combined by the tissue protoplasm, but this is gradually set free and is usually excreted in from two to three days, Cloetta, 1903. The excretion begins at once and can be detected both in the saliva and in the secre-

¹ Faust, Edwin S.: *Archiv f. Pathologie und Pharmakologie*, Bd. 44, S. 217-238, 1900.

tions of the stomach within a few minutes after its injection. In dogs even the vomit produced shortly after hypodermic injections, and as a result of morphine, has been shown to contain excreted morphine. A trace of morphine is excreted by way of the kidney.

With continuous use of morphine the oxidizing power of the tissues increases, thus leading to a degree of tolerance which is very marked. A chronic opium user will consume enough morphine at a single dose to kill one unaccustomed to the drug. Faust tested the basis for this tolerance. He gradually increased the daily hypodermic dose of morphine hydrochlorate given a 6.7 kilo dog. The initial daily dose was 0.045 grams. After ten weeks the animal received daily 2.5 grams, all of which was oxidized. On the 86th day 3.5 grams produced only a general "soporific" condition. A dose of 1.5 grams of morphine is toxic to a normal dog of the weight of the one used by Faust. Faust expresses the belief that the apparent tolerance is in reality ability to oxidize, and that the tissues do not become non-responsive to the alkaloid.

Codeine is also excreted in large per cent. unchanged, in this case also through the feces, but to a larger extent through the urine. Tolerance is not acquired for codeine to the same degree as for morphine.

VI.

The Abuse of Opium.

Opium has been used for ages as a means of producing physiological and psychological states considered more or less desirable by the victim. Opium is used for smoking, in snuffs, and for eating. A favorite means of using morphine is by hypodermic injections. The chronic user is striving for the mental effects that characterize the earlier stages of morphine action.

The Oriental peoples are the chief abusers of the members of this series, especially in the East Indies and in China. In fact the use of opium in China was forced as a commercial proposition and stands to the discredit of the English people. At the present time, in the United States, there is a considerable use of opium for smoking, and of morphine taken by the method of hypodermic injection.

The smoking of opium is a favorite method among the "opium victims." It produces a mental state or intoxication in which the individual experiences an elation characterized by dreamy yet vivid imaginings. The individual use of the drug would not be

so deplorable except for the fact that there is a marked tendency for habit formation, from which it is next to impossible to escape. The tissues of the body acquire increased oxidizing power and a tolerance for the drug, and along with this an irresistible demand for it. The victim has no power of resistance. He not only requires the drug, but will obtain it at the sacrifice of all the moral and intellectual restraints which modern society ordinarily holds inviolable.

The effect of chronic opiumism on normal metabolism is very great. Morphine interferes with the usual oxidation processes. This depresses growth and development, leads to degeneration and weakness, in short, contributes to the general bodily degradation. Under this condition the body is in a real pathological state, therefore morphinism must be looked upon from the standpoint of disease. The tissues in such condition reach a state in which the total deprivation of morphine becomes intolerable to the victim. The only way to relieve him is by the gradual reduction in the amount of morphine, associated with the best of conditions favorable to normal nutrition. In practice this has been found to be possible only in special sanatoria where the physiological needs of the individual are supplied, and at the same time he is put under restraint that yields the control of practical imprisonment.

VII.

Condensed Summary of the Action of Morphine and the Opium Series.

Morphine is a narcotic and sedative, acting primarily on the central nervous system. It produces a mild but brief stimulation, followed by a decrease in function of the cerebral cortex, beginning with the higher psychic centers and acting in a descending direction. In the nerve centers of the medulla the most profoundly influenced is the respiratory center, which, after a brief acceleration, diminishes in sensitiveness and is ultimately paralyzed by toxic doses. The spinal cord is decreased in its sensitiveness to reflex stimulation, but in the late toxic stages, especially in the lower animals, often shows a decreased resistance, bordering on the convulsive. The circulatory system is markedly depressed in its efficiency. Blood-pressure falls, due in the early stages to slowing of the heart through the action of the inhibitory center and to peripheral vasodilation, but in the later stages to direct depression of the cardiac rhythm and to vasodilation

through loss of vasomotor control. The pupil is constricted, but this passes into dilation with the final toxic stage.

Morphine produces nausea and vomiting chiefly through central action on the vomiting center. It produces an initial increase in the peristalsis of the alimentary tract, followed by marked depression of alimentary efficiency because of contraction spasms of the pyloric stomach. The initial stimulation is slight in man, but very marked in certain mammals where morphine often leads to marked purging as well as vomiting. The depressing effect on peristalsis is due to depression of the extrinsic nerves controlling the alimentary tract, coupled with stimulation of the local mechanism. Morphine lowers metabolism, diminishing the excretion of nitrogen. It also influences special metabolisms, such as the glycogenic function of the liver. Morphine is excreted chiefly through the alimentary canal, 70 per cent. A trace is eliminated by the kidney and there is some oxidation by the tissues. Oxidation increases with prolonged use, and tolerance is acquired for morphine largely through increased oxidative powers and the adaptation of the tissues to its presence. In extreme tolerance the daily quantity used may reach ten times an ordinary toxic dose. Other members of the morphine series, in the order of increasing methyl substitution, as in codeine and thebaine, produce similar, though less intense narcotic effects, but with greater stimulation. In thebaine the stimulative action, especially on the spinal cord, approaches the convulsive.

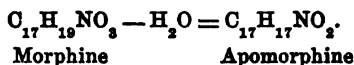
CHAPTER VIII.

APOMORPHINE AND APOCODEINE.

I.

Historical and Chemical.

Certain drugs produce emetic effects so definitely and characteristically that they have come to be used in therapeutics for that action alone. Of these, one of the best known and characteristic is apomorphine. Apomorphine is derived from morphine by dehydration which can be accomplished by various dehydration agencies such as acid, etc., according to the formula:



In this chemical treatment the characteristic morphine actions are largely lost and there is a strong stimulating action developed in regard to special mechanisms in the central nervous system.

Apocodeine is derived from codeine by similar treatment, which produces a loss of water from the molecule.

II.

Outline of Pharmacological Action.

1. *Apomorphine produces a strong stimulation of the vomiting center in the medulla which is specific.*
2. *Stimulation of secretory centers for saliva, perspiration, etc.*
3. *Paralytic action on skeletal muscle.*
4. *Marked depression of cardiac muscle.*
5. *Apocodeine is strongly paralyzing to the nerve paths in peripheral ganglia, poisoning at the same point as nicotine.*
6. *Apocodeine is toxic to all forms of motor nerve endings.*

III.

Details of Pharmacological Action.

Morphine itself has a twofold action which, in its discussion, has been described in some detail, namely, a stimulating action, and a

depressant action. In its transformation into apomorphine the alkaloid has lost practically all of its latter pharmacological properties, but has retained the property of stimulating, especially for certain portions of the nervous tissue.

1. **On the central nervous system.**—Apomorphine acts chiefly stimulative to the medullary centers controlling the glands and the alimentary canal. This action is specific on the vomiting center. A hypodermic injection of eight to ten milligrams will produce nausea and vomiting in man in ten to twelve minutes. After vomiting the symptoms ordinarily rapidly disappear. The premonitory changes are a feeling of weakness, increase in the secretion of saliva and of perspiration, and a feeling of warmth over the skin. With larger doses there may be repeated vomitings followed by languor and a certain degree of collapse. The dangers from apomorphine are relatively slight, depending largely on a tendency to paralysis of the motor centers.

Other nerve centers in the medulla are sharply stimulated by apomorphine. For example, experiments on mammals show that the respiratory center is also accelerated and that an animal will breathe a relatively greater volume of air in a unit of time under the influence of this drug. This is in marked contrast to the action of morphine, which produces the opposite effect on the respiratory volume, notwithstanding the incipient respiratory acceleration. All those glandular mechanisms under the control of the nervous system, such as the salivary and buccal glands, the glands of the respiratory tract, the sweat glands, the lachrymal glands, etc., are set into vigorous secretion. Apomorphine is therefore an active expectorant and diaphoretic. There is some evidence of increased spinal sensibility, which shows itself in the accelerated general activity of such animals as the cat. However, the excitation which this animal shows, quite characteristic under morphine also, may be explained on the assumption of some degree of hyperirritability of its nervous mechanisms, i.e., of the higher centers.

In animals which do not have well developed the ability to vomit, the stimulating action of apomorphine is readily demonstrated by its action on other portions of the central nervous system. Such animals become restless and more active, but their movements are uncoördinated. The cat, for example, shows an increased motor activity quite comparable to its behavior under morphine itself. In the late stages, following strong doses, nervous paralysis sets in, the reflexes are lost and death may follow from respiratory failure.

All the symptoms associated with apomorphine emesis are readily explained on the assumption of marked stimulation of the vomiting mechanism. This mechanism can be set into action physiologically by increasing the irritability of the sensory cells in the peripheral region, as for example in the mucous membrane in the stomach, or by direct action on the nerve cells in the vomiting center of the medulla. Violent irritation of the stomach mucosa, as for example by such irritants as mustard, strong salines, tartar emetic, etc., all result in the reflex production of vomiting. In the case of apomorphine, however, vomiting results as readily when the drug is given hypodermically as when given internally. Eggleston and Hatcher¹ have recently made a re-study of the question under the title, "The seat of the emetic action of apomorphine." By a guarded series of experiments they come to the conclusion "that all of the evidence favors the view that apomorphine acts directly upon such central mechanism," i.e., the central controlling vomiting mechanism. Further, "that apomorphine acts solely by direct stimulation of the central vomiting mechanism in the dog and probably also in man." From their published experiments the following table of the effective apomorphine dose for the dog is compiled:

Apomorphine dose for the dog (Eggleston and Hatcher).

Method of Giving Apomorphine	Milligrams per kilo	Time before Emesis
Stomach.....	5.7	8 minutes
Subcutaneous.....	0.2	7½ minutes average
Intramuscular.....	0.075	4 minutes
Intravenous.....	0.045	

2. The depressant action on muscular tissue.—Apomorphine depresses the irritability of skeletal muscle, as can readily be shown on the muscles of the frog. This effect is of significance on man, only where extremely toxic doses may have been given, since respiratory failure may be contributed to by the muscular paralysis.

The heart is weakened from direct and toxic depression of the cardiac muscle.

¹ Eggleston and Hatcher: *Journal of Pharmacology and Experimental Therapeutics*, Vol. III., p. 551.

IV.

Apocodeine.

1. The action of apocodeine on nervous structures.—Dixon¹ has published an exhaustive study of the pharmacology of apocodeine. He shows that all the numerous systemic effects which are observed after the display of this drug can be explained as due directly or indirectly to the toxic action on nervous tissue. For example, the injection of apocodeine, 1 to 2 mgr. per kilo, for a dog, leads to a marked fall of blood-pressure to a relatively low level, associated with a more rapid heart rate, and accompanied by evidence of vascular dilation in the periphery. If nicotine has previously been used, then these effects do not follow apocodeine. Also with the latter drug there is no initial rise of blood-pressure indicative of vascular stimulation as with nicotine. At the same time drugs which influence the peripheral nerve endings, like epinephrine, continue to be active. It is obvious that the circulatory changes can be explained on the assumption that the nerve cells of the ganglia on the course of the autonomic fibers have lost their function, have been poisoned.

After somewhat stronger doses of apocodeine the post-ganglionic fibers of the various autonomic paths are no longer functional. Stimulation of the accelerator nerves of the heart or of the splanchnics does not give rise to cardiac acceleration or to visceral vasoconstriction. Yet drugs, like digitalis and barium chloride, which influence the peripheral tissues, are still active (Dixon). All these observations indicate that the toxic influence of apocodeine is general for motor nerve endings. However there is a degree of selective action in that visceromotor and cardiac inhibitory nerves are paralyzed by the weaker doses, the voluntary motor and the accelerator nerves of the heart by medium doses, and vasomotor by toxic doses of the alkaloid. For the cat 60 to 70 mgrs., given intravenously, eliminates the function of the cardiac ganglia, 100 to 120 mgrs. the vagus endings, and 250 to 300 mgrs. the cardiac accelerator nerve endings.

2. On the alimentary canal and urinary motor system.—The paralysis of the nervous mechanism of the alimentary canal and of the urino-genital system leaves the motor structures of those systems free to give out their normal automatic contractions. The result is that the stomach, intestine, and urinary bladder are all thrown into increased muscular movements. This reaction led Dixon to suggest the use of apocodeine for the purpose of increasing smooth muscle

¹Dixon, W. E.: *Journal of Physiology*, Vol. XXX., p. 97, 1903.

contractions in cases of motor stagnation from over-inhibitory nerve stimulation.

3. Apocodeine in support of pharmacological investigation. —After all, at the present time, with apocodeine as with nicotine, the value of the drug has been most striking in relation to scientific research. Rational medicine undertakes to demonstrate the exact reactions in the body produced by medicinal agencies. The extraordinary complexity of the animal body has proven baffling in relation to the study of changes effected by many of the drug agencies. The discovery of a drug, which can definitely throw out of function the peripheral nerve endings of the autonomic system makes it possible to reinvestigate those drugs the action of which have been problematical, as for example pilocarpine, epinephrine, digitalis, etc.

V.

The Action of the Irritant Emetics.

Emesis can also be produced reflexly by other substances. In this case any sufficiently irritant substance in contact with the gastric mucosa leads to a violent gastric irritation along with the excessive development of sensory stimuli. The effect of these stimuli, when of physiological intensity, is favorable in the stimulation of the nerve centers controlling the glands which pour their secretion into the alimentary canal, and which to some degree favor the development of alimentary peristalsis. When the stimuli become excessive all the medullary centers, including the vomiting center, are overstimulated.

Try Fig 74, Dixon, u. 275.

Of these peripheral acting emetics there is a large series, but the following may be mentioned as the most important:

Warm water,	Mustard,
Strong sodium chloride solution.	Tartar emetic,
Ipecac,	Zinc sulphate, etc.

B. General Stimulating Series.

CHAPTER IX.

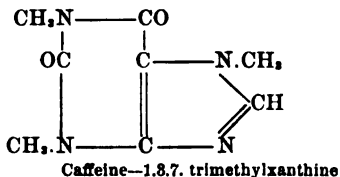
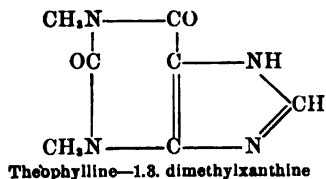
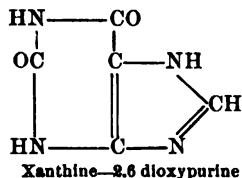
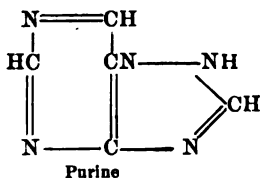
THE CAFFEINE GROUP.

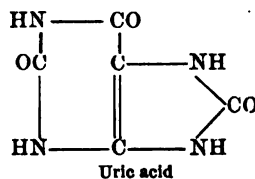
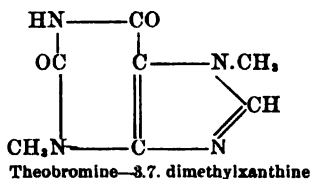
I.

Historical and Chemical.

Caffeine and its relatives are vegetable alkaloids which are chemically related to the purine-xanthine products of the animal body. The most widely used and best known of this group are caffeine, derived from the coffee berry, *Coffea Arabica*, and from the leaves of the tea plant, *Thea Chinensis*; and theobromine, derived from the seeds of *Theobroma Cacao*, which is a tree native to Central and South America. Tea leaves contain also theophylline. Several other plants contain small quantities of these alkaloids, of which may be mentioned the cola nut of Africa, *Cola acummata*, which contains caffeine and theobromine.

The chemical relationships of these alkaloids to the purine bodies is shown in the accompanying structural formulæ of xanthine (dioxypurine), theophylline (1.3. dimethylxanthine), theobromine 3.7. dimethylxanthine), and caffeine (1.3.7. trimethylxanthine).





II.

Outline of Pharmacological Effects.

Caffeine is one of the purest stimulating agencies acting on physiological mechanisms which, has thus far been described. Its primary effects are:—

1. *The excitability of the central nervous system is increased in the descending direction, stimulation primarily of the cerebral cortex and later the centers of the spinal cord and the medulla.*
2. *It increases the power of muscular contraction of all kinds of muscle.*
3. *It is a cardiac and vasomotor stimulant.*
4. *Caffeine is a vigorous diuretic.*

III.

Details of Pharmacological Effects.

1. **Caffeine on the central nervous system.**—The alkaloids of the caffeine group increase the irritability, and therefore the volume of the reactions, through the central nervous system at all points. Its stimulating effect falls, first and primarily, upon the cerebral cortex, especially on the higher psychic functions of the association centers of the cortex. It increases the delicacy of sensory perception by increasing the sensitiveness of the mechanisms of the cortex. As a result a given sensory stimulus produces a greater volume of psychic reaction during caffeine than before the use of this drug. The association of ideas is facilitated. As a net result, the ability to do mental work and the volume of work done are both increased. It is evident that caffeine produces a change in the nervous complex, which facilitates the passage of nerve impulses, hence there is a tendency to alertness and fatigue is displaced by a feeling of comfort. But, while caffeine is favorable to the greater production of psychic activity under stress, attention must be called to the fact that such a nervous whip is not without its exhausting after effects.

The amount of physical work which a man can do depends, not only upon his muscles, but upon the neuro-muscular mechanism as a whole. Caffeine by its influence upon the nervous side of the machine alone, greatly increases the amount of physical work and endurance. Thus, in modern army regulations the well-known beneficial effects of caffeine are recognized by the addition of coffee to the ration during the execution of forced marches. A part of this influence of caffeine falls upon the muscular tissue, as will be explained later, but the main effect is in the stimulation of the central nervous system.

With larger and especially with excessive doses of caffeine, extreme restlessness and nervous excitability occur and severe headache develops. In extreme cases there is some confusion of thought with a tendency in the toxic intensity of action to delirium and convulsions. Many individuals are hypersensitive to caffeine and cannot endure the larger doses to which the average person gives only a moderate response.

2. **The spinal cord.**—Caffeine and other members of the group add to the sensitiveness of the spinal cord. Reflex excitability is increased, though not to anything like the extent produced by strychnine. Even the lower vertebrates show a greater response to cutaneous stimulations, in some cases approaching tetanus. These effects are shown more delicately on toads, *Bufo*, than on the usual laboratory frog, *Rana esculenta*, partly due to the characteristic motor activities of the former.

3. **The medulla.**—Caffeine stimulates the nerve centers of the medulla, especially the cardiac inhibitory and the respiratory centers. In the case of the respiratory center the alkaloid apparently acts directly on the nerve cells, greatly increasing their sensitiveness. Respiratory stimuli, therefore, produce markedly greater discharges of motor nerve impulses. The respiratory rhythm is also sharply accelerated.

4. **The action of caffeine on the skeletal muscle.**—Caffeine increases the amount of muscular work which can be voluntarily accomplished, as shown by ergographic records. A percentage of this beneficial effect is due to central nervous action as previously mentioned, but apparently the larger part is due to the influence of the series on the muscular tissue. The most striking demonstration of this point is had from parallel records from the work of two gastrocnemii. If one muscle be allowed to absorb caffeine through the normal circulation while the other is kept free from the drug, and if parallel records be taken of the contractions in response to repeated stimuli

of the same intensity applied to each muscle, it will be found that the drugged muscle will do from ten to thirty per cent. more work than the normal muscle. Skeletal muscle is also rendered more sensitive to stimuli so that the minimal stimulus has a smaller intensity in a caffeinized muscle. Larger, i.e., toxic, doses produce a persistent contraction and rigor, a fact that is of diagnostic value in distinguishing between caffeine and strychnine in physiological toxicology.

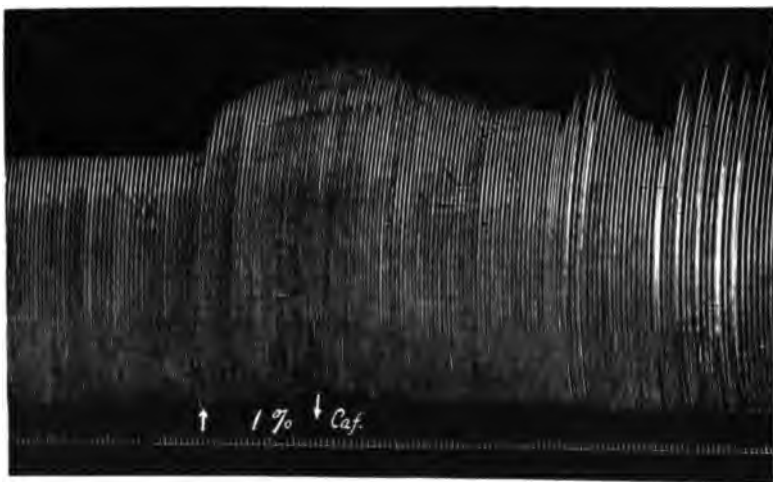


FIG. 22.—The influence of caffeine 0.1 per cent. in blood-Ringers solution on the contractions of the isolated heart of a cat perfused through the coronary arteries. The irregularity which appears in the last portion of the tracing continued to increase, showing periodical groups of extremely rapid rhythm. The regular rhythm was soon re-established. On repeating the experiment the rhythm was enormously increased and accompanied by even a more marked increase in amplitude. Time in seconds. New tracing by Boutwell, Miller, and Peeler.

cology. This rigor can be produced by the different members of the series, including xanthine itself.

Smooth muscle and cardiac muscle are similarly influenced by caffeine.

5. **Caffeine on the circulation.**—The effect of caffeine on the general circulation is to produce a rise of blood-pressure. The degree of change is influenced by the somewhat antagonistic physiological effects of the stimulation of different parts of the circulatory mechanism. Therapeutic doses of caffeine produce a favorable rise, while the strong doses are apt to be followed by irregular results. This is explained by the details which follow.

6. **Caffeine on the cardiac mechanism.**—Caffeine and the other members of the series stimulate both the nervous mechanisms controlling the heart and the cardiac muscle, as shown in heart strips and in the isolated mammalian heart. There is an increase in the rhythm and a stronger contraction. This increases the discharge of blood from the ventricles, both from the increased volume of a single beat and from the increased number of beats for a unit of time. Undoubtedly this favorable influence on the function of the heart is due to direct action on the muscular tissue. This is proven by the influence of caffeine on isolated ventricular muscle from the lower animals.

Xanthine, which is a product liberated in the mammalian body, also markedly stimulates the mammalian heart as shown by Kobert.

Strips of terrapin's ventricle produce stronger contractions, and usually an acceleration of rhythm when bathed in graded strengths of solutions of caffeine. This favorable activity on the heart muscle is also shown in the perfused isolated frog's heart preparations where the amplitude is markedly increased and the rate slightly accelerated. In the frog's heart there is a tendency to systolic contracture, especially in the late stages of the after effects. Cushny has demonstrated the favorable action of caffeine on the heart by direct records from the heart of mammals *in situ*. Caffeine produces both acceleration and increased amplitude under these conditions.

The heart rhythm is often slowed by therapeutic doses of caffeine. This apparently contradictory action is due to a preponderant stimulation of the vagus center in the medulla. In the therapeutic dose the medullary stimulus is greater than the direct cardiac, hence there is relative slowing. By laboratory experiments it can be shown that minimal inhibitory stimuli for the vagus become subminimal after the injection of caffeine, which is due to the greater activity of the cardiac muscle and not to depression of nerve function.

7. **Caffeine on the vasomotor apparatus.**—The vasomotor apparatus is stimulated by caffeine both centrally and peripherally. The vasoconstrictor center is set into greater tonic activity, which leads to increased peripheral constriction. The drug also produces a greater irritability of the smooth muscle, which adds to the peripheral constriction of the arterioles. Hence there is a marked increase in the vascular resistance with a corresponding rise of blood-pressure. With excessive doses this peripheral constriction amounts to a vascular spasm, and may thus influence the reactions of the tissues in secondary ways.

8. **The action of caffeine on the respiratory mechanism.**—The acceleration of the discharge of nerve impulses from the respiratory center under the influence of the caffeine series was mentioned while discussing the medulla. But the favorable reaction is in part due to the peripheral influence on the respiratory muscles. In all marked depressions of the respiratory mechanism, as from alcohol or in morphine narcosis, caffeine forms a splendid antagonistic drug. Considerable quantities of caffeine may be administered in such cases without running the risk of collapse in the after stages, of the kind which characterizes the effects of over-stimulation from strychnine.

9. **Caffeine on metabolism.**—The study of the central nervous system, of the musculature, and the great circulatory and respiratory mechanisms, all indicate greatly increased functional activity under the influence of caffeine. It is obvious that metabolism in these special tissues is accelerated thereby. The metabolic increase is further indicated by the greater output of carbon dioxide and of nitrogen, and also by the rise in general body temperature.

10. **The diuretic action of caffeine.**—Therapeutic quantities of caffeine, and especially of theobromine, produce marked diuresis in man and the mammals. The diuretic action may increase the output of urine per unit of time several hundred per cent., as demonstrated by Cushny on the rabbit. In man this increase may amount to fifty per cent. or more. Associated with the greater water output, there is an increase in the solids of the urine, both inorganic and organic.

Considerable discussion has arisen as to how the favorable influence of caffeine is accomplished. By some it is held that the diuretic action is secondary to the favorable action on the circulation. This, however, will scarcely account for the greater volume of urine sometimes observed in low blood-pressure. It is more probable that the caffeine members act to increase the irritability of the renal epithelium in a way not unlike their action on muscular and nervous tissue. With toxic doses of caffeine there is occasionally complete suppression of the urine, a result that is explained by the production of arterial spasms with shutting off of an adequate renal blood flow.

11. **The absorption and excretion of caffeine.**—The alkaloids of the caffeine series are readily absorbed from the alimentary tract. They are excreted by the kidney, but only in small part unchanged. The greater part of the caffeine undergoes oxidation in the body, with loss of methyl, being converted into dimethyl or into monomethyl-

xanthine. The xanthine of caffeine origin is undoubtedly further oxidized in the body in the same way as the xanthine of animal origin.

IV.

Condensed Summary of the Action of the Caffeine Group.

Caffeine is a primary nerve stimulant. Its action is characterized by descending stimulation, falling first upon the cerebral cortex and later upon the centers of the medulla and spinal cord. It produces a primary acceleration of psychic activity, a greater sensitiveness to the inflow of stimulation, which arouses, or at least supports, intellectual work. Caffeine also stimulates the motor nervous mechanisms of the spinal cord and the medulla. It increases the power of the skeletal muscle to do muscular work. Therefore it has a favorable influence over conditions of fatigue and exhaustion, coupled with a minimum of deleterious after effects. Respiratory activity is markedly accelerated, due to increased sensitiveness of the respiratory center and in part to an increase in the irritability of respiratory muscles. The circulation is favorably augmented by a rise of blood-pressure, and a slightly slower but stronger heartbeat. Heart muscle itself is rendered more irritable and its contractions more vigorous, but in therapeutic doses of caffeine, the stimulation of the inhibitory center overcomes the muscular acceleration. The arterioles are constricted, partly from direct muscular action and partly from increase in the tone of the vasomotor center. Metabolism in general is favored and the body temperature increased. Diuresis is produced by caffeine through primary stimulation of the renal epithelium. Anuria may result from an overstimulation by the production of stricture of the arterioles. Caffeine loses its methyl and is oxidized down to monomethyl xanthine and uric acid in which forms it is largely excreted. A portion may be excreted unchanged.

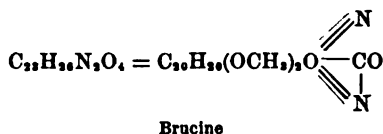
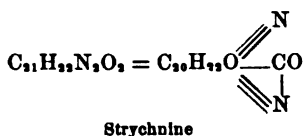
CHAPTER X.

THE STRYCHNINE GROUP.

I.

Chemical and Historical.

Strychnine is an extremely toxic alkaloid, found together with its relative brucine in the various species of *Strychnos*. These alkaloids are present in the largest quantity in the seeds, but are also found in portions of the bark and wood. The best known species from which the alkaloids are obtained are *Strychnos nux vomica*, and *Strychnos ignatia*. The seeds of *Ignatia* contain about two per cent. total alkaloid, three parts strychnine, and one part brucine, of *nux vomica* from 2.6 to 3.9 per cent. of the two alkaloids, about equally distributed. Strychnine is much more toxic than brucine, in about the ratio of 1 to 50. The chemical formulæ of the two alkaloids are:



The brucine differs from strychnine in that it contains two oxy-methyl groups. Both alkaloids are very insoluble in cold water, but they readily form salts, which are soluble.

II.

Outline of Pharmacological Action.

1. *Strychnine increases the irritability of the spinal cord and the central nervous system.*
2. *It causes convulsions and tetanus in toxic doses.*

3. *It increases the sensibility of special sense organs.*
4. *Tonic reflexes are produced by the bitter taste.*

III.

Details of Pharmacological Action.

Nux vomica has for a long time enjoyed a favorable reputation as a vigorous stimulating agency. Hypodermic preparations of the strychnine salts are given more or less indiscriminately in emergency cases, not only as legitimate nerve tonics, but too often on the mistaken theory that they are vigorous cardiac stimulants. With strychnine, as with numerous other medicinal agencies, there has been a tendency to generalize the use of the drug from insufficient data. Strychnine is, as a matter of fact, a tremendous nerve stimulant. On the other hand, its use on the heart and circulatory system as an emergency stimulant is partially, if not wholly, irrational.

1. **The spinal cord and brain-stem.**—With strychnine in therapeutic quantity, up to 2 milligrams of strychnine nitrate, there is a great increase in the reflex irritability of the centers of the spinal cord and brain-stem. This produces an increase in the susceptibility to the ordinary normal stimuli with a corresponding increase in the volume of discharge of motor nerve impulse. The slight acceleration of the cerebral cortex and of the higher nerve centers, produced through the action of this factor, is relatively insignificant.

Strychnine action on the spinal cord seems almost specific, in that the effect is selective on the spinal structures. If the brain be removed strychnine still produces the same qualitative effects. Reflexes take place through the cord in response to milder stimuli than in the normal, and there is a tendency to the involvement of larger and larger areas of cord until, with toxic doses, even the mildest stimulus entering at any sensory point, may set the whole neuro-muscular mechanism into tetanic spasms.

By tetanic convulsions one understands spasmodic and persistent contractions of the entire voluntary musculature. The individual muscles exhibit series of very rapidly following contractions with imperfect relaxations. The usual well coördinated alternate contractions of the opposing muscles no longer occur, but instead, the extensors contract at the same time and stronger than the flexors. The effect is that the trunk and limbs are thrown into an extended position. The entire body thus becomes stiff and rigid. The muscular cramps involve the respiratory mechanism, hence, when they follow

each other too rapidly they tend to produce asphyxia. Man and mammals usually die after a short series of convulsions, largely because of an asphyxial paralysis of the respiratory center. Frogs may endure tetanic contractions for days and even weeks, due to the fact that adequate respiration is maintained through the skin in these animals.

In attempting to explain the mechanism of the strychnine cramps, it has been shown that complete severance of all the sensory nerves

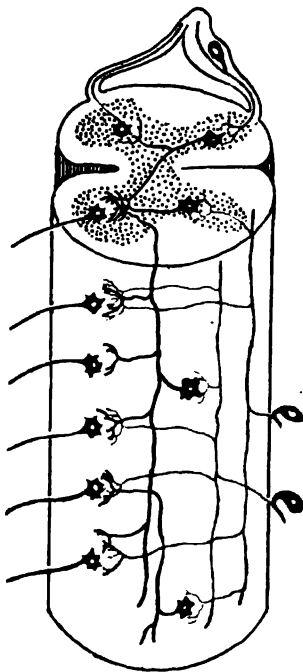


FIG. 23.—Von Kölliker's scheme of neuron relations in the spinal cord. Orange, afferent or sensory; red, efferent or motor; and black, central or connecting neurons.

leads to failure of the development of the spasms. Central stimulation of the end of a sensory nerve sets up strychnine contractions. In like manner, cocainization of the entire skin will eliminate strychnine spasms when the body is otherwise so sensitive that even a slight current of air is sufficient stimulus to initiate the contractions. It is perfectly evident that sensory stimulation is necessary to the development of the tetanic contractions, but that the tetanus does not depend upon the toxic change in that mechanism. Houghton and Muirhead¹

¹ *Medical News*, 1895.

determined experimentally that strychnine specifically poisoned the receptive, i.e., connecting, neurons of the spinal cord. They exposed the spinal cord of the frog, having excluded the circulation, and painted a local area with strychnine solution. The area painted soon became hypersensitive, showing the usual general tetanic responses to cutaneous stimulation. The tetanus involved, not only the local area, but also the motor area of the unpoisoned parts of the cord. On the other hand, stimulation of portions of the skin connected with an unpoisoned portion of the cord led only to the usual normal reflexes. Since direct stimulation of the motor cells themselves cannot produce tetanic spasms, it is to be inferred that the toxic influence falls especially on the connecting nerves lying between the afferent sensory and efferent motor neurons of the cord. The alteration of the protoplasm produced in these cells by strychnine does not lead to automatic discharge of nerve impulses by the cells in question, but the cells are rendered so very unstable that the least sensory stimulus sets them into maximal discharges. The nerve impulses are strong enough to break down the usual physiological resistance to the diffusion through the differential mechanisms of the cord.

Sherrington¹ has called attention to the physiological fact that the stimuli leading to contractions of the flexor muscles of the body are associated with inhibitory processes for extensor muscles, and vice versa. Whenever an extensor is reflexly stimulated the flexor will be inhibited. In other words the stimulative processes for an agonist are associated with an inhibition of the antagonist. Strychnine undoubtedly destroys this normal antagonistic action of the two sets of muscles. One may assume that in strychnine tetanus the physiological resistances through the cord which maintain the balance between the agonistic and antagonistic groups are so broken down by the drug that all power of coördinative reaction is lost.

This general effect of strychnine characterizes the reaction of the entire vertebrate series, though the sensibility of the cold-blooded animals is considerably less than that of the mammals.

2. *The medulla.*—Strychnine produces similar changes in the medulla to those noted in the spinal cord, though the cord is more sensitive to the drug than the medulla. The nerve centers of greatest importance in this connection are the respiratory, the vasomotor, and the cardiac inhibitory centers. These are all increased in sensitiveness by the therapeutic action of strychnine, hence give a greater volume of response to the usual sensory stimuli.

¹ Sherrington: Phil. Trans. Royal Society, 1898, Vol. CXG., p. 160.

3. **On respiration.**—The influence of strychnine is to increase the respiratory activity due to the increased sensitiveness of the respiratory center and the central connecting mechanisms of the cord involved in respiratory movements. Strychnine is therefore in therapeutic quantity a good antagonist for pathological or pharmacological effects which tend to depress the central mechanism of the respiratory apparatus. The converse holds under restricted limits only. That is, the late or toxic paralysis of strychnine must be guarded against, lest

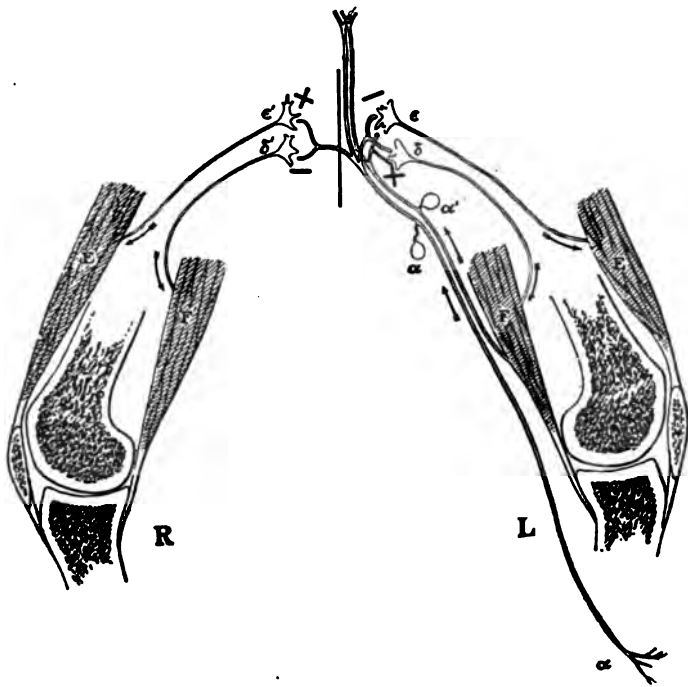


FIG. 24.—Sherrington's diagram to indicate the anatomical basis for the physiological control of stimulative and inhibitive processes in the spinal cord. R. and L., right and left pairs of antagonistic muscles. α , α' , afferent paths, which, when stimulated, produce coincident stimulations, +, and inhibitions, —, as shown. This orderly reaction is broken down by strychnine.

this stage of its action be additive to that produced by the primary acting narcotic.

4. **On the circulation.**—Therapeutic doses of strychnine produce changes in the circulatory apparatus only by causing variation in the delicacy of response in the central portions of the nervous mechanism controlling the heart and blood-vessels. This point cannot be too

strongly emphasized, owing to the general and often indiscriminate practice of administering strychnine in cardiac emergency.

The heart is indeed influenced in its rhythm and amplitude, but only through changes in the reflex sensitiveness of the cardiac centers of the cord and medulla. In the otherwise normal animal the heart, as a rule, contracts with a somewhat slower rhythm and stronger amplitude, typical of increased vagus activity. The changes in the heart rhythm under ordinary tonic and therapeutic doses of strychnine, are relatively insignificant; in the subtoxic doses permissible in mammalian experiments the heart rate is often markedly slower. This statement is applicable to experiments on the otherwise normal animal under surgical anesthesia. If a mammal be curarized and artificial respiration be maintained, then the variation in cardiac rhythm under the influence of strychnine may be demonstrated.

The curarized animal is especially instructive in other regards. For example, in a mammalian experiment, on the animal used in the experiment represented in Figure 25, there were intermittent periods of very slow cardiac rhythm, alternating with periods of striking acceleration. Considering the fact that strychnine following nicotine and atropine, which together eliminate the function of the major portion of the autonomic system, produces no change in either cardiac rhythm or blood-pressure, it is a logical deduction that the drug is acting through the controlling nervous mechanisms. Further, strychnine produces its changes through the central portions of these nervous mechanisms. Referring back to the alternate retardation and acceleration of the heartbeat mentioned above, it is obvious that these two nerve mechanisms are both strongly influenced by strychnine, i.e., by action on the centers. Slight variations in external conditions may give one mechanism the controlling hand at one time, the other at another time, since both vagus and accelerator centers are known to be in tonic action.¹

Cardiac muscle, on the contrary, is not only not stimulated, but decidedly depressed both in amplitude and rhythm under the influence of strychnine. If, for example, the frog's heart be perfused with strychnine solution, its rhythm and amplitude are both decreased. Following normal perfusion, there is a very slow and prolonged but gradual recovery from the toxic effects on the cardiac protoplasm. Similar reactions are noted on the isolated mammalian heart. The amplitude of its contractions is depressed without a preliminary rise.

It would seem from the above facts and arguments that the bene-

¹ Hunt, Reid: *Jour. Exp. Med.*, Vol. II., p. 151, 1897.

ficial effects of strychnine on the circulatory system, that have been claimed in therapeutic practice, must rest wholly on the changes in the reaction delicacy through the central nervous mechanisms. By an increase in the irritability of the cardiac inhibitory and acceleratory centers, normal stimuli may produce more profound and beneficial changes in the musculature of the cardiac apparatus. It must be remembered, however, that even this favorable cardiac re-

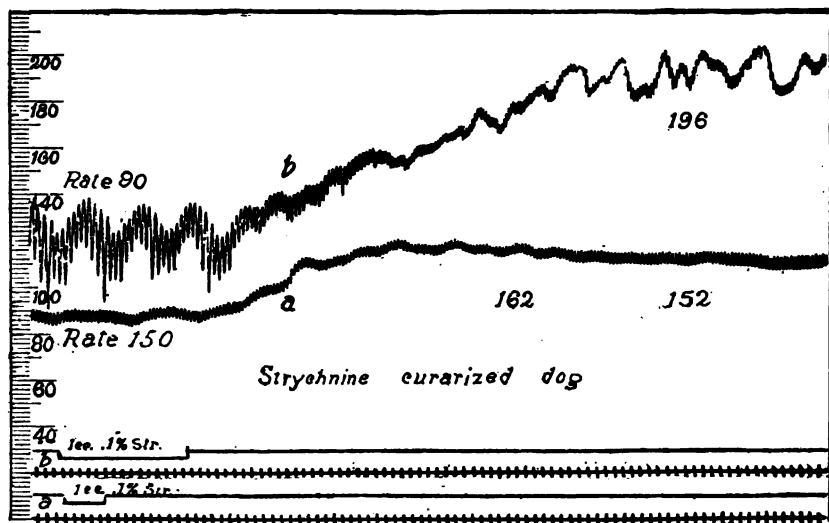


FIG. 25.—The action of strychnine on the vascular nervous complex as shown in the blood-pressure and pulse changes. Two experiments, *a* and *b* are presented in this figure. The experiment was performed on an ether anesthetized dog under the influence of curare, and with artificial respiration. Experiment *a* shows the influence of an initial dose of 1 mg. of strychnine injected into the venous system. Experiment *b* represents the effect of a repetition of this dose after several minutes. Between *a* and *b* the pulse rate varied greatly, showing periods of slow rhythm, as indicated in the initial rate in *b*, interspersed with periods of extremely rapid rhythm. The slow rhythm at the beginning of tracing *b* is due to inhibition. Gross variations in blood-pressure independent of respiratory rhythm occurred. These are well shown in *b*. In a succeeding test during a period of slow rhythm the vagus nerves were cut, the heart rate leaped forward to 210 per minute. The scale to the left measures the pressure in experiment *a* from a zero at the time line at the bottom. The zero and time line of experiment *b* falls on the 20 millimeter pressure level of the first experiment, hence, deduct 20 millimeters of mercury to read the scale for *b*. Time in seconds. New tracing by Kruse, Boutwell, and Heldt.

sponse to strychnine is somewhat antagonized by the depression of the cardiac muscle tissues.

In a similar way the vasomotor center is found to be more sensitive to reflex stimulation when under the influence of strychnine. This leads to an increase in blood vascular tone, though the benefit is relatively more slight than the changes induced in the heart. In the tetanic stage of the reactions of skeletal muscle it is claimed that the

vasomotor center is also thrown into tetanic discharge, thus producing vascular cramps. A slight rise of blood pressure is usually noted during the muscular tetani, a fact also explained on mechanical grounds, i.e., through the mechanical pressure changes in the abdomen and thorax. My experience is that the mechanical factors play a very small part in vascular changes induced by strychnine. This fact is borne out by the influence of strychnine after nicotine and atropine. Although muscular cramps will be produced as usual, they are not accompanied by more than slight mechanical changes in blood-pressure.

5. On skeletal muscle.—The greater volume of muscular contractions noted in an animal, when under the influence of strychnine,

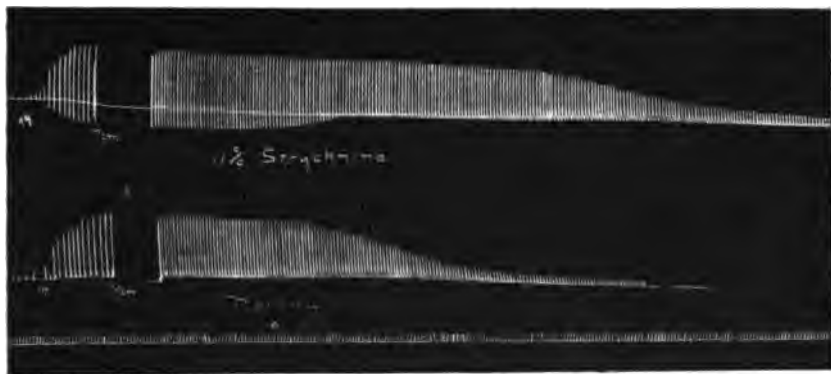


FIG. 26.—Strychnine on muscle irritability and muscle work. Little change is shown on irritability of the muscle, but the work is increased. Frog 18 grams, dose 0.1 cc. of 0.1 per cent., allowing 10 minutes for absorption, load 75 grams. Time in 2 second intervals. New tracing by Summers.

has generally been explained as due wholly to the influence of the alkaloid on the central nervous system. However, parallel experiments on the amount of work which the isolated gastrocnemii of a frog will do under rhythmically repeated stimuli applied directly to the muscle, show that the strychninized muscle will accomplish a greater amount of work than the normal muscle. In fact, the muscle substance becomes somewhat more sensitive to stimuli; in other words, the minimal stimulus on the drugged muscle is reached by a stimulus of weaker intensity. It has not yet been clearly shown whether the muscle substance or the "receptive substance" is really the point of favorable action. In the toxic stage strychnine produces a paralysis of the motor end plates in a way comparable to curare, with which the drug is chemically related. This last point suggests that

the receptive substance may be the point stimulated in the therapeutic dosage.

6. **Action on the special sense organs.**—Experimentation has produced cumulative results indicating a definite beneficial influence on the sensitiveness of the special sense organs. The sense of smell is rendered more acute, and a change in the character of odors has been noted. In the same way the senses of sight and of hearing are rendered more acute, the usual tests of hearing are perceived at a greater distance than normally, and the visual field is enlarged. The sense of touch is rendered more delicate. This increase in delicacy is noted both in relation to the strength of the threshold of the stimulus and in the accuracy of localization. However, it is not clear just what portion of the sensory mechanism is acted upon by the drug. We are inclined to believe that the change is chiefly, if not wholly central rather than peripheral, though unilateral action claimed for the eye cannot be explained by this view.

7. **On the alimentary canal.**—Strychnine has long enjoyed a reputation as a bitter tonic. This is due primarily to the extremely bitter taste, which can be detected one part in 600,000, but there is a factor of systemic action involved. The bitter taste leads to profound physiological reflexes involving the mouth and gastric glands, also the motor apparatus of the stomach. When strychnine is absorbed, even in extremely small quantity, the secretory and gastric motor mechanisms of the central nervous system are rendered more susceptible to stimuli, hence an increase in tone results. The general influence on metabolism, especially of sluggish tissues, as in vascular and in alimentary atony, is favorable.

8. **On metabolism.**—Since strychnine produces a general rise in tonus of the neuro-motor mechanisms of the body and increases the volume of response to the usual stimuli, it is obvious that it will produce a general rise in metabolic activity. There is a tendency to a rise of body temperature, though it is controlled by the heat regulating mechanism. The increased metabolism is secondary rather than primary. Hence skeletal muscle, the plain muscle, and the glands are thrown into greater activity through the greater delicacy of poise of the centers of the central nervous system.

Strychnine is fixed by the tissues of the body, probably by the lipoids. Koch suggests that the intensity of action of strychnine bears a relationship to the percentage of lipoids in the particular tissues most strongly influenced by the alkaloid.

9. **Excretion.**—Strychnine is excreted unchanged in the urine,

although a portion is greatly delayed in its excretion, due to its fixation in the tissues, and a proportion is ultimately oxidized. This latter point was established by Meltzer, who found that nephrectomized rabbits were able to withstand strychnine in toxic amounts, provided it were given in broken doses.

IV.

Strychnine Poisoning.

The too frequent cases of strychnine poisoning make it desirable to discuss the antidotes and treatment. Accidental and suicidal poisoning usually occurs by the method of taking the drug into the stomach. The first step then is to produce evacuation of the stomach, either by vomiting or by means of the stomach pump. Precipitants such as tannic acid or strong tea may be given for temporary fixation of the strychnine, but this must be removed just the same. Strychnine is not readily absorbed from the stomach, but disappears readily when it reaches the intestine. After convulsions have begun or are approaching, it may be very difficult to introduce the stomach tube. A slight spray of cocaine in the mouth-pharynx region is beneficial or ether or chloroform may be given lightly, in order to pass the tube.

Evacuation of the stomach should be followed up with systemic treatment, which consists in the use of antagonists, such as ether or a small quantity of chloral. Ether is preferable to morphine because of the greater ease of its control. Chloral and morphine by their prolonged action become dangerous in the paralytic stage of strychnine action.

Meltzer has recently emphasized the value of artificial respiration in strychnine poisoning. The administration of large quantities of fluid and of diuretics is favorable, though the excretion of strychnine is relatively slow at best.

Brucine.

Brucine has an action very similar to that of strychnine except that it is much weaker. It requires a dose of brucine about fifty times larger to produce similar effects. In one regard, brucine is relatively more toxic, namely, in its curare-like paralysis of the motor nerve endings.

Thebaine, one of the alkaloids of opium, it must be remembered, has also an action similar to strychnine. It also brings on strychnine-

8. The action of caffeine on the respiratory mechanism.—The acceleration of the discharge of nerve impulses from the respiratory center under the influence of the caffeine series was mentioned while discussing the medulla. But the favorable reaction is in part due to the peripheral influence on the respiratory muscles. In all marked depressions of the respiratory mechanism, as from alcohol or in morphine narcosis, caffeine forms a splendid antagonistic drug. Considerable quantities of caffeine may be administered in such cases without running the risk of collapse in the after stages, of the kind which characterizes the effects of over-stimulation from strychnine.

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III.

Details of Pharmacological Action.

1. **Specific action on the motor nerve endings.**—Curare owes its physiological action almost exclusively to the specific toxic paralysis of the connecting substance, linking motor endings and skeletal muscle. This fact was demonstrated in the middle of the last century by Claude Bernard, 1857, by the method which has become classic in physiological literature. The method slightly modified as now practiced is: First, shut off the circulation in one leg of the frog by a ligature around the thigh, excluding the sciatic nerve; second, inject curare into the lymph sacs and allow absorption to take place, whereby the alkaloid passes into the general circulation, going into all parts of the body with the exception of the muscles and tissues of the ligated leg. Paralysis of all the voluntary mechanisms takes place. The point of action of the drug is demonstrated by the following steps in the physiological analysis:

1. Stimulation of the sciatic nerve of the curarized leg produces no contraction of its muscles.

2. Stimulation of the sciatic nerve of the unpoisoned side below the point of the ligature naturally produces contractions, since no drug has come into contact with this part of the apparatus.

3. Stimulation of the sciatic nerve of this side above the ligature, where the nerve has been irrigated by the blood containing the curare, also produces contraction of the muscle, showing that the nerve fibers are not directly poisoned.

4. Upon direct stimulation of the muscle of the poisoned leg contraction results, demonstrating that the curare has not paralyzed the contractile muscle substance.

Bernard drew the conclusion that the toxic effect is upon the protoplasmic substance of the motor end plates, for which, therefore, the poison is specific.

Kühne later, 1886, gave a beautiful demonstration in this way: He noted that the motor nerve of the gracilis muscle of the frog branches before it enters the muscle. By cutting the muscle between the two branches a double preparation is secured, in which the parts are innervated by one nerve, but the end plates and muscle substance form two physiologically separate preparations. When curare is painted on one preparation stimulation of the common nerve fails to produce contraction in that division only. When the

poisoned muscle, with its contained nerve filaments, is stimulated and recurrent conduction carries the nerve impulse around, and never fails to produce contractions in the unpoisoned slip. Excessive use of curare later destroys the irritability of these nerve filaments, indicating that nerve fiber does ultimately succumb to the poison.

Langley¹ has more recently examined the point of action of curare. He argues that the poison is not toxic to the nerve endings, but rather is toxic to a differentiated secondary constituent of the muscle fiber, which he designates the "receptive substance," a substance that receives the stimulus from the nerve and transmits it to the proper contractile substance. Strength is given his position by the fact that curare antagonizes certain muscle-stimulating substances after motor nerve degeneration occurs.

Bernard showed also that the sensory mechanism of the reflex arc is not injured by ordinary doses of curare. Stimulation of the skin on the poisoned side of the curarized frog leads to reflex contraction of the muscles of the unpoisoned leg. If the sensory nerves in the skin were paralyzed such a reaction would be impossible.

2. Curare on peripheral ganglia.—Strangely enough curare does not poison the striated muscle of the heart, though large doses do eliminate the function of the vagus nerve. This effect is accomplished by a poisoning of the pre-ganglionic connections around the cells of the cardiac ganglia, a nicotine-like effect. Other autonomic ganglionic endings are similarly poisoned by large doses of curare, as, for example, the vasomotor paths, the secretory nerves of the salivary glands, and the nerves controlling the muscles of the iris and ciliary apparatus.

Curare leads to a fall of blood pressure in the mammal because the paralysis of the pre-ganglionic endings eliminates vasomotor tone. Such effects are not very profound, nothing comparable to the intensity of action on the skeletal motor nerve relations.

3. Absorption of curare from the stomach.—It has long been known that curare is comparatively inactive when taken by way of the stomach. There is a sharp contrast as between the intensity and rapidity of action from subcutaneous administration. Hence its inertness in the stomach has called for explanation. Several views have been offered, but that of Bernard is most probable and would account for the facts. Bernard's view is that the absorption takes place so slowly from the stomach and that the active principle of

¹ Langley, J. N.: *Journal of Physiology*, Vol. XXXIII., p. 374, 1905.

the drug is excreted so rapidly that its toxic effects do not materialize. Some evidence has been found to show that curare is destroyed either by the digestive action of the stomach or by the changes that occur during absorption. Another factor enters here, namely, the fact that the venous blood from the stomach passes through the liver where the parenchyma tends to fix this alkaloid as it does many others. This would hold back the passing of curare into the general circulation, hence would be favorable to its elimination before a fatal toxic action took place.

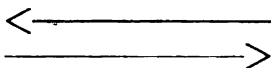
IV.

Comparison of Curare with Related Drugs.

Curare stands at one end of the series of drugs and nicotine at the other as follows:

Nicotine, coniine, gelseminine, sparteine, curare

Ratio of stimulating effect on the central nervous system and of paralysis of peripheral ganglia.



Relative toxicity to peripheral nerve endings.

Nicotine produces preliminary stimulation of considerable intensity followed by marked paralysis. Curare produces practically no central stimulation. Nicotine has slight effect on peripheral nerve endings. Curare has pronounced and specific toxic effects on the endings (or receptive substance) of skeletal muscle. Nicotine and curare both are toxic to peripheral ganglia, though nicotine is much more toxic than curare.

There are a number of drug groups which have characteristic actions on peripheral parts of the nervous mechanism, and sometimes on particular motor nerve tissues. These drugs interfere with physiological activity by a selective combination with the differentiated structures of some portion of the parts of the body involved. They are in the highest degree specific in action. Their specificity depends upon a greater chemical affinity with the physiologically differentiated constituents of certain morphological structures. It is not to be understood that the reaction is limited exclusively to these

parts and that other portions of the body are inert toward the drug, but rather that the degree of selection depends upon the greater intensity of action at some particular morphological point. In the therapeutic use of such drugs it is comparatively easy to accomplish a change in the function of the part specifically attacked great enough to be of clinical value without materially interfering with the functions of other non-specific reacting parts of the body. Of this series the most characteristic from the pharmacological point of view are atropine, nicotine, coniine, curare, and the pilocarpine series.

CHAPTER XII.

THE ATROPINE SERIES.

I.

Historical and Chemical.

The atropine series contains a number of alkaloids of extremely bitter taste, found in the plants of the order Solanaceæ. Of the species yielding alkaloidal principles should be mentioned *Atropa*, *Datura*, *Duboisia*, *Hyoscyamus*, etc.

Atropa belladonna, deadly nightshade, contains atropine, hyoscyamine, and hyoscyne.

Datura stramonium, or thorn apple, contains atropine, hyoscyamine, and hyoscyne.

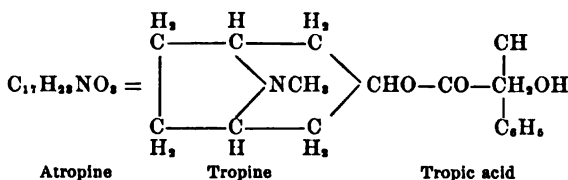
Duboisia myoporoides, contains duboisine and hyoscyne.

Hyoscyamus niger, or henbane, contains atropine, hyoscyamine, and hyoscyne.

Mandragora autumnalis, or mandrake, contains mandragorine, and hyoscyamine.

Atropine itself is extracted chiefly from the roots and leaves of the plant *Atropa belladonna*. It is associated with hyoscyne and hyoscyamine.

The drug is readily decomposed into tropine and tropic acid. Hyoscyamine is isomeric with atropine; in fact, atropine is now considered to be a mixture of dextro- and levo-rotary hyoscyamine. The chemical relationship of the elements is expressed in the formula:



II.

Outline of Pharmacological Action.

1. *Paralysis of the peripheral endings of the secretory nerves, the cardiac inhibitory nerves, the constrictor nerves of the pupil, and of the motor nerves of the stomach and intestine.*

2. *Initial stimulation of the motor apparatus of the alimentary canal and urinary bladder, thought to be muscular.*

3. *Mild initial stimulation of the cerebral cortex and of the centers of the brain-stem and cord, followed by depression and later by paralysis.*

4. *Toxic direct paralysis of the medullary centers.*

III.

The Details of Pharmacological Action.

Other alkaloids of the atropine series differ in their effects from atropine only in a mild quantitative way. Hence the description of atropine will serve as a type for all the members of the series.

1. **General symptoms of the action of atropine.**—The therapeutic dose of atropine is from 0.5 to 1 milligram. These or slightly larger doses produce in man a perceptible acceleration of the heartbeat, a mild dilation of the pupil, a general dryness of the throat and skin, accompanied by difficulty in swallowing, thirst, and general discomfort from the lack of secretions of the mouth and nasopharyngeal region. If the symptoms are severe there is nausea, occasionally dizziness, and general mental discomfort.

There is an initial slight increase of cerebral functions, which passes into incoherence, garrulousness, delirium, or semi-consciousness, but without loss of muscular control. In extreme cases there may be convulsions. In toxic conditions this effect may be followed by deep stupor, labored respiration with a tendency to asphyxiation, and even asphyxial death. This general picture is complicated by the specific peripheral effects of atropine expressed in combination with those on the central nervous system.

2. **Action of atropine on the central nervous system.**—The evidences of stimulation and excitement with the respiratory and circulatory disturbances indicated above show that atropine has a profound influence on the central nervous system. Unlike caffeine, which acts primarily on the higher cortical centers, and strychnine, which acts earliest on the spinal cord, atropine produces its effect through a general more uniform action on the whole nervous system—a little more profound on the medulla, if any distinction is to be drawn. In the later or more intense stages of atropine action, the motor side of the central nervous mechanism is the more profoundly influenced, and it is this that leads to increased physical activity, garrulousness, or convulsions. In animal experimentation one rarely observes

cortical nervous accelerator effects due to atropine. Von Bezold and Blöbaum¹ first established the stimulating action of atropine upon the respiratory center. They injected atropine peripherally into the carotid artery, so that the alkaloid was first brought into direct contact with the central nervous mechanism. They noted an immediate quickening of respiration. This effect would seem to

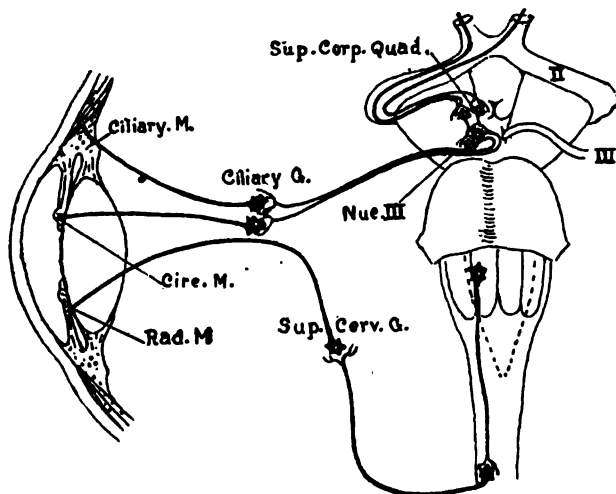


FIG. 27.—Diagrammatic representation of the nerves of the intrinsic muscles of the eye. *Sup. Corp. Quad.*, superior corpora quadrigemina. *Nuc. III*, nucleus of the third cranial nerve. *Sup. Cerv. G.*, superior cervical ganglion. *Circ. M.*, circular muscles of the iris. *Rad. M.*, radial muscles of the iris. *Ciliary G.*, ciliary ganglion.

follow from the direct action of atropine upon the respiratory center, a fact that has been confirmed. There was also an increase in the respiratory volume of from 100 to 300 per cent. The primary effects of atropine are followed by a deep depression of function with ultimate paralysis of the central nervous system. The paralysis of the respiratory medullary center may, if artificial respiration is maintained, be overcome. The life of the animal is thereby prolonged, and the recovery, if it occurs, is due to the fact of rapid oxidation of atropine by the tissues.

3. **The specific action of atropine on the eye.**—Atropine applied to the eye locally produces dilation of the pupil and loss of the power of accommodation. The toxic systemic effects on the respiratory center are produced before complete loss of function of the accommodating mechanisms occurs, hence in practical ophthalmology it is

¹ Von Bezold and Blöbaum: *v. Bezold's Untersuchungen*, Vol. I., 1877.

customary to apply atropine by dropping it on the surface of the eye in a one per cent. solution. After about 15 minutes the effects are maximal and last for many hours.

The ciliary mechanism and the iris of the eye are innervated by two sets of nerves, as shown in the Figure 27. The third cranial or oculomotor nerve distributes branches to the muscles of the ciliary apparatus, and the circular muscles of the iris. Stimulation of this nerve leads to an act of accommodation adjusting the eye for near vision, and to a constriction of the pupil. The cervical sympathetic also distributes branches to the eye. These innervate the radial muscles of the iris and produce dilation of the pupil when stimulated.

The loss of the power of accommodation from local application of atropine is explained on the ground of a toxic paralysis of the nerve endings of the oculomotor fibers on the ciliary muscles.

The dilation of the pupil can be accomplished physiologically by either of two methods: contraction of the radial fibers through stimulation of the cervical sympathetic nerve, and relaxation of the circular fibers by elimination of function of the oculomotor. A direct paralysis of the circular muscles in the absence of effect on the radials would, of course, accomplish a dilation of the pupil. That atropine does not poison the muscles themselves can be easily shown by the response of the muscles of the iris to stimulation by the direct application of electrodes. It would seem, therefore, that in the local application of atropine to the eye the functional disturbance is due to paralysis of the oculomotor nerve. Direct stimulation of the oculomotor nerve either proximal or distal to the ciliary ganglion, is no longer effective after the application of atropine. This indicates a poisoning in the junction between the nerve and the muscle, according to Langley's views at the "receptive substance."

The paralysis of the nerve endings of the ciliary mechanism of the eye by atropine persists for two or three days, and often for six to ten days in the case of the iris. The artificial alkaloid, homatropine, produces the same ocular effects, but is not so persistent, hence is to be preferred under certain therapeutic conditions.

4. **The specific action on glands.**—The dryness of the mouth and throat produced by atropine is due to a decrease in the secretions of the salivary and other buccal glands, as well as those of the throat. Atropine accomplishes this effect by an elimination of the control of the secretory nerves. Since direct stimulation of the chorda tympani or of the tympanic branch of the hypoglossal produces no secretion of the salivary glands, it is apparent that the action of

the drug is peripheral. The stimulation of the cervical sympathetic in the dog still produces its scanty secretion after atropine. Here, therefore, as in the eye, only one set of nerves is paralyzed, and that by a toxic elimination of the function of the terminal nerve endings and not by paralysis of the gland cells.

Other glands have their secretion diminished by atropine, especially the gastric, pancreatic, and to a much less extent the mammary glands. Thanks to the work of Pawlow, we now know that the gastric glands produce their secretion under a well-coördinated nervous control. The vagus is proven to be the secretory nerve for the gastric glands. Atropine produces a profound inhibition of gastric secretion, both in the Pawlow dog and in man (Riegel).

In like manner atropine in weaker doses inhibits the pancreatic secretion. Modrakowski¹ has emphasized the fact that very large doses of atropine in the dog call forth a voluminous pancreatic secretion—a fact difficult of explanation by the laws of nerve control. The secretion of pancreatic juice, which is controlled through the hormones, indicates that hormone reaction, in general, is not interfered with by atropine.

In the case of the secretion of milk, the therapeutic action of atropine is demonstrated clinically, though in the present state of our knowledge of the physiological mechanism of the mammary glands, it is not fully understood what structure the atropine affects. The development of these glands and of lactation at parturition are phenomena dependent on hormone actions, and are quite independent of nerve control, as is now well known.

Atropine paralysis occurs in the nerves of the sweat glands. Langley has shown that the sciatic nerves contain secretory fibers for the sweat glands of the foot of the cat and the dog, where he has mapped their distribution. After atropine poisoning these nerves no longer induce secretion. It follows that atropine must be toxic to the nerve endings of the sweat fibers.

5. On the circulatory system.—There is a slight rise of blood-pressure following atropine, together with an increase in the rate of the heart. Experimental investigations of the peripheral circulation show that atropine has little effect on the size of the arterioles, except in toxic concentrations. There is a reddening of the skin, with evident vascular dilation just at the beginning of its systemic action, whether due to a paralysis of the vasoconstrictor center or a stimulation of the vasodilator center is not yet determined. In ex-

¹ Modrakowski: *Pflüger's Archiv*, Vol. CXIV., p. 487.

periments on the salivary glands the stimulation of the chorda tympani, which contains vasodilator fibers, produces an increased flow of blood through the glands, though the increase is not associated with a secretion of saliva. This well-known experiment shows that the endings of the vasodilator nerves are not paralyzed, but are active in the presence of an amount of atropine toxic to the secretory endings.

On the other hand, the nervous mechanism of the heart is profoundly influenced. Atropine produces an elimination of the in-

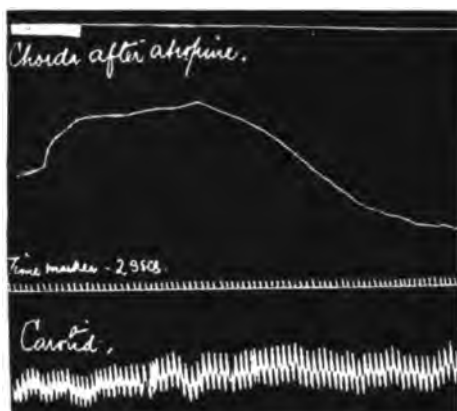


FIG. 28.—Stimulation of the chorda tympani after the administration of 10 mg. atropine. The carotid pressure, lower line; volume of sub-maxillary gland, second line from the top. The volume of the gland increased, showing that atropine does not eliminate the vaso-dilator nerve function. After Bunch.

hibitory control of the vagus over the heart. When atropine is given systemically the vagus control is lost, and the heart is accelerated in the same way as though the vagus nerves were sectioned in the neck. Whereas stimulation of the peripheral end of the vagus nerve in the normal animal produces more or less inhibition of the heart, after atropine such stimulation of the vagus, and indeed of the region of the sinus, is without influence on the heart, showing a loss of the vagus control at the neuro-muscular unions. Therapeutic doses of atropine have little accelerator effect on the heart rate of very young animals or of young children, due to the fact that the vagus tone is less developed in the young.

The heart muscle itself is very little affected by atropine. In isolated muscle preparations from the terrapin's heart a wide range of concentration of atropine in solution in physiological salines may

be applied to the tissue with little or no effect on the rate. There is much irregularity in the results, but the accelerations are about balanced by the depressions which occur. Doubtless it is these irregularities that have led to the contradictory statements that have

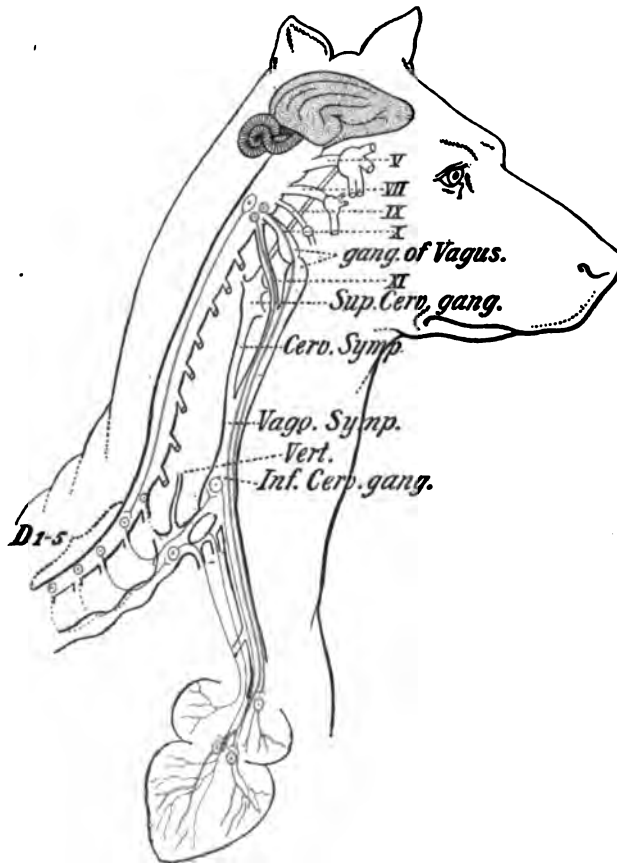


FIG. 29.—Diagrammatic representation of the origin and course of the cardiac nerves in the dog, showing the constituent neurones. D1-5, first to fifth dorsal spinal nerve. Inhibitory fibers in blue, accelerators in red. Modified from Moret.

appeared in the literature concerning the effects of atropine on the cardiac muscle.

6. **Atropine on the alimentary canal, the stomach.**—The peristalses of the stomach are under the control of the vagus, which is the motor nerve for this organ. Atropine produces an inhibition of the contractions. Minute doses apparently are not entirely toxic to the local nervous mechanism, but they do eliminate, at least depress, the

motor control of the vagus endings. The preponderant inhibitory tone of the splanchnic apparatus in the absence of the motor activity of the vagus leads to a cessation of the gastric peristalses, a fact of especial therapeutic interest in the practical use of this drug.

The intestine.—The motor apparatus of the intestine is also paralyzed by atropine, though there is some contradiction in the literature in this case. Very small therapeutic doses occasionally increase peristalsis by stimulation of the smooth muscle (Jacobj), or of the ganglion cells like nicotine (Langley and Magnus). In a general way atropine reacts on the intestine in much the same way as on the stomach. Meltzer and Auer¹ say, "Atropine frequently abolished completely the vagus effect upon the stomach and reduced greatly its effect upon the intestines."

7. On the bladder and uro-genital apparatus.—The urinary bladder and the uro-genital system are controlled through nerves arising in two different regions of the spinal cord. One set arises from the lumbar region, the fibers passing out in the third to the fifth ventral roots of the lumbar nerves. They run thence through the sympathetic chain and hypogastric nerve. The other nerves arise from the lower sacral cord, the second to the fourth sacral nerves, and run to their distribution by way of the nervi erigentes.

Langley and Anderson² found variations in the physiological responses of the uterine walls given in different animals when the hypogastric nerves were stimulated. Dale³ later demonstrated that upon stimulation of the hypogastric in the non-pregnant cat there was generally a relaxation of the muscular walls of the uterus. But in the rabbit sometimes there was relaxation and sometimes contraction of the muscles. If the test was made on a pregnant animal the response was always a contraction of the muscular walls, sometimes followed by peristalsis. In the male the muscular walls of the vasa deferentia and seminal vesicles are set into contraction by the stimulation of the hypogastric nerve. It will be remembered that this nerve contains the vasoconstrictor fibers for the blood-vessels of all these organs. Atropine does not abolish the functional nerve control of the uterus on the one hand or of the seminal vesicles on the other.

¹ Meltzer and Auer: *American Journal of Physiology*, Vol. XVII., pp. 143-166, 1906.

² Langley and Anderson: *Jour. Physiol.*, Vol. XIX., p. 127, 1895.

³ Dale, H. H.: *Jour. Physiol.*, Vol. XXXIV., p. 189, 1906. See also Cushny: *Jour Physiol.*, Vol. XXXV., p 1.

The innervation of the bladder is twofold. Fibers reach it by way of the hypogastrics as mentioned above, and through the *nervi erigentes*. Stimulation of the hypogastric leads to contraction of the muscular walls of the bladder, chiefly of the sphincter. The sacral nerves, i.e., the *nervi erigentes*, it will be remembered, are the special paths of vasodilator fibers. They also supply motor fibers to the bladder as well as to the constrictor urethræ. "The sacral nerves cause contraction of all the muscle fibers of the bladder, whether they are circular, oblique, or longitudinal."

Langley and Anderson question the presence of inhibitory fibers in the muscular walls of the bladder, stating that "few, if indeed any, exist." Atropine in large doses acts to reduce the sacral motor control over the bladder, apparently acting in a way comparable to its influence on the nervous control of the stomach and intestine. It does not completely eliminate the nerve control, that is, it does not completely poison the endings. The depressing effects produced, even with comparatively large doses, are not very great, not enough to eliminate the nervous control. There is indeed a slight but questionable stimulation of the smooth muscle and possibly of the nerve centers of the cord after mild therapeutic doses of atropine. In the urinary bladder, especially in the hypersensitive conditions, which occasionally occur in children, this atropine quiescence leads to a better retention of the urine. In the uterus atropine suspends peristaltic contractions. It is not clear just what phase of the nerve-muscular mechanism is primarily influenced by the atropine, but the present tendency is to assume a similarity of action to that which occurs in other better known physiological mechanisms, as, for example, the eye.

8. **Atropine excretion.**—Atropine is excreted through the kidney. It has been shown by Fleischmann, 1910, and confirmed by Metzner, 1912, that atropine is destroyed by the blood of the rabbit, even in mixtures in the test tube. Atropine breaks down into tropine and tropic acid. This capability probably accounts for the fact that the rabbit is able to resist such large quantities of atropine. However, this animal may have acquired some degree of immunity from eating plants of this series.

IV.

Condensed Summary of the Pharmacological Action.

The changes in physiological reaction in the human body upon the introduction of atropine are relatively complex because of the num-

erous secondary disturbances of the physiological balance. In small, i.e., therapeutic doses, there is a dryness of the mouth and throat from a decrease in secretions, a slight increase in physiological reactions through the nervous system, excitement followed by a tendency in the toxic stage toward irrational mental reactions, with garrulousness, unconsciousness, and even convulsions, followed by stupor and paralysis. Respiration is accelerated slightly, then depressed and stopped by central paralysis. Blood-pressure is at first increased, through stimulation of the regulative nerve centers, the heart shows initial very slight inhibition, followed by increased rate of beat from terminal paralysis of the vagus. There is little direct effect upon heart muscle. The blood-vessels in the toxic stage are dilated and blood-pressure falls. The general voluntary motor apparatus is finally depressed and paralyzed through action on the motor nerve cells. Atropine produces a slight initial stimulation of smooth muscle in various localities, followed by a depression of peristaltic contractions. This is true for the intestine, urinary bladder, and uterus.

Scopolamine or hyoscine has a greater depressor effect upon the various portions of the central nervous system and the autonomic nerve centers. It enjoys a certain amount of prestige in cases of mania, and also as a depressor of hyperexcitable sexual centers.

CHAPTER XIII.

THE PILOCARPINE, MUSCARINE, PHYSOSTIGMINE GROUP.

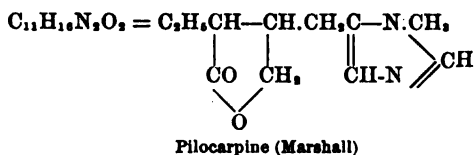
Under this head may be included a series of active alkaloidal principles which have a strong peripheral stimulating effect. In the main these drugs produce their action at the point of nerve terminations in differentiated tissues.

I. PILOCARPINE.

I.

Historical and Chemical.

Jowett¹ has shown that the leaves of *Pilocarpus jaborandi* and of other species of the genus contain only three alkaloids, pilocarpine, iso-pilocarpine, and pilocarpidine, the last named only in small quantity. Harnack and Meyer² have given us the composition of pilocarpine, but the structural formula is quoted from Marshall:



II.

Outline of Pharmacological Action.

1. *A strong stimulation of glandular structures—the salivary, bronchial, lachrymal, and gastric glands, and the liver.*
2. *A similar stimulation of the smooth muscle of the eye, of the*

¹ Jowett: *Jour. Chem. Soc.*, 1900, Vol. LXXVII., pp. 473, 851; 1901, Vol. LXXIX., pp. 580, 1,331; 1903, Vol. LXXXI., p. 438.

² Harnack and Meyer: *Arch. f. Exp. Path. u. Pharm.*, 1880, Vol. XII., p. 366.

alimentary tract, the urinary bladder, the spleen, and of the bronchi, but little or no stimulation of the muscles of the blood-vessels.

3. *A slight stimulation, followed by marked depression, of the centers of the central nervous axis.*

III.

Details of Pharmacological Action.

1. **The stimulation of the glands.**—In therapeutic dose, 5 to 8 mgr. for man, pilocarpine leads to a marked increase in the secretions.

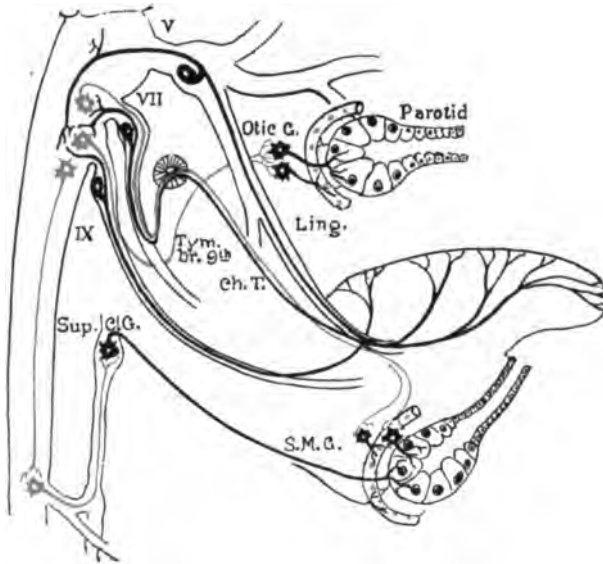


FIG. 30.—Diagrammatic representation of the neurones in the innervation of the salivary glands. V, VII, and IX, the corresponding cranial nerves. Ch. T., chorda tympani containing secretory and vasodilator fibers, also, according to certain authorities, gustatory nerve fibers; Tym. Br. 9th, tympanic branch of the 9th cranial nerve containing secretory and vasodilator fibers for the parotid gland; Otic G., Otic ganglion; Ling., lingual branch of the 5th; Sup. C. G., superior cervical ganglion of the sympathetic; S. M. G., submaxillary ganglion. Some of the neurones through this ganglion belong to the sublingual gland. Preganglionic neurones in red, also the central neurone in the cord. Postganglionic neurones and sensory neurones in black. Diagram based on figures by Sheldon, Brubaker, and Starling.

These are most striking in the salivary glands, sweat glands, and the mucous glands of the mouth and throat. The gastric and pancreatic secretions are also increased. The liver produces an increased amount of sugar, leading to glycosuria, which suggests that this organ too is stimulated by the pilocarpine.

The amount of saliva and of perspiration produced is enormous,

amounting to several hundred cubic centimeters more than the normal. Ewing¹ has made a special study of the quantity and chemical composition of the saliva in man produced under the stimulus of pilocarpine. He records an instance in which a normal 15-minute secretion of 37 cc. of saliva was increased to 563 cc. in the third 15-minute period after 10 mgrs. of pilocarpine. He also demonstrated that the

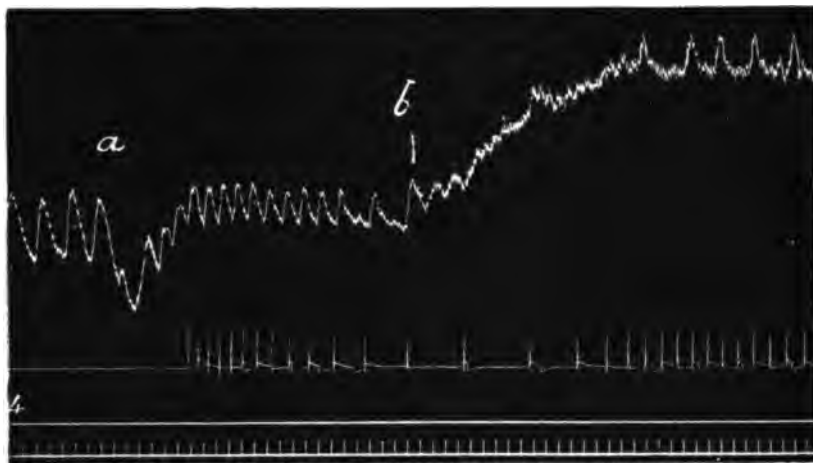


FIG. 31.—Influence of 0.2 mg. pilocarpine on the rate of secretion of saliva. The drops of saliva are recorded in the second line from the top. At *a* injection of pilocarpine, at *b* injection of 50 cc. of oxygenated blood. From Jonescu.

total amount of solids, both organic and inorganic, keeps pace with the increase in the total secretion.

The glands are stimulated through the nervous mechanism. Since the secretion occurs after section of the nerves but is absent when the nerve endings are paralyzed by atropine, it is assumed that the pilocarpine reacts with the substance of the terminations of the nerve fibers, as has been advocated by Langley.² However, Langley has more recently arrived at the conclusion that pilocarpine reacts with a differentiated portion of the gland cell, the "receptive substance," which is the linking up substance as between the fibrils and the secreting gland substance. He finds that the sweat glands of the foot produce secretion after sectioning of the sciatic nerve.

The kidney and the mammary glands are not particularly influ-

¹ Ewing, E. W.: *Jour. Pharm. and Exp. Ther.*, 1912, Vol. III., p. 1.

² Langley, J. N.: *Journal of Physiology*, 1905, Vol. XXXIII, p. 374.

enced by pilocarpine. This is due undoubtedly to the fact that these organs do not have a well-developed nervous controlling mechanism. Any influence which is exerted on the two organs is probably due, therefore, to indirect effects through the vascular system. Pilocarpine influences the flow of blood through the glands, and this, together with the increased production of sugar by the liver, would account for the observed increase in sugar in pilocarpine milk.

2. **Pilocarpine on the circulatory apparatus.**—Pilocarpine injected intravenously leads to a marked fall of blood-pressure. The fall is secondary to a marked inhibition of the rate of the heart.

3. **The heart.**—Pilocarpine leads to slowing of the heart in both the frog and the mammal. This may reach a complete inhibition

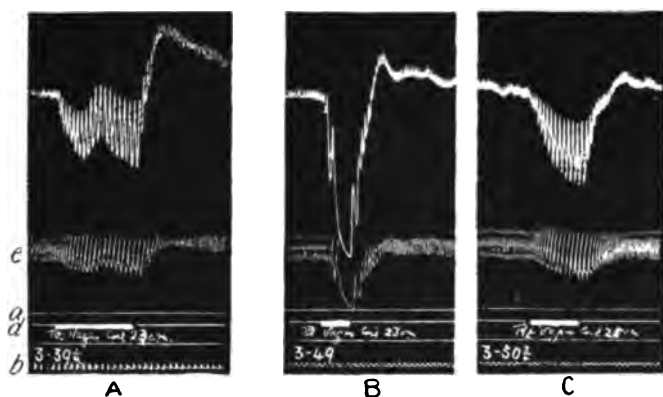


FIG. 32.—Showing the increased sensitiveness of the vagus control in the cat after administration of 0.1 milligram of pilocarpine. The right vagus was cut, peripheral end stimulated, the induction coil at 25 cm. showed no inhibition, at 20 cm. marked inhibition before the drug was applied. A, right vagus stimulated 23 cm. normal; B, same stimulation after pilocarpine; C, stimulation at 25 cm., after pilocarpine. The increased sensitiveness of the vagus gradually wore off. a, pressure base line; b, time in seconds; d, duration of stimulus; e, Hurtle's manometer record. The top tracing shows the blood-pressure. From Marshall.

as the action of the drug proceeds. The cardiac slowing is due to a stimulation of the vagus terminations, since it occurs after section of the vagi; in fact, after paralysis of the vagal ganglia. Marshall¹ has shown that small doses of pilocarpine at once depress, then quickly increase the response of the vagus to stimulation. The reaction is an additive one, since the drug and the electrical stimulation produce the same end effect on the cardiac apparatus.

Pilocarpine, curiously enough, when taken by the mouth is associated with an increase in the pulse rate noted quite constantly in

¹ Marshall, C. R.: *Journal of Physiology*, 1904, Vol. XXXI, p. 150.

man. This has been variously explained. By some it is considered as a direct stimulation of the cardiac accelerator endings. But others, notably Marshall, consider it a secondary effect. This latter is probably the safer explanation.

Pilocarpine and atropine are antagonistic in their cardiac effects, though the former is only about one-twentieth as vigorous in its toxic action.

4. **The blood-vessels.**—Pilocarpine has little effect on the blood-vessel mechanism in comparison with its more profound glandular action. Given intravenously, the marked fall of blood-pressure suggests vasomotor paralysis. The pressure change, however, is chiefly due to cardiac slowing at this stage. There is some slight vasomotor action, but not enough to overcome the cardiac slowing. Perfusion of isolated organs (Dixon) shows vasoconstriction. The later and more toxic action leads to paralysis of the vasomotor center.

5. **Pilocarpine on the respiratory tract.**—In addition to its nerve effects, pilocarpine produces a contraction of the bronchial musculature, which tends to interfere with the free respiratory movements, making them more or less labored. In this instance, as in many pharmacological situations, a chain of secondary influences supervenes. The great increase in the secretions of the respiratory passages produces an increase of mucus, etc., that tends to block the smaller tubes interfering profoundly with the respiratory interchange.

Studies indicate that the total respiratory exchange, especially the output of carbon dioxide, is increased under the influence of pilocarpine. This is to be expected because of the great increase in functional activity of glandular and other motor tissues.

6. **On the central nervous system.**—At first pilocarpine is slightly stimulative to the nerve centers of the medulla and cord. After larger doses there is a tendency to paralysis and collapse, especially of the medullary centers. The respiratory center is markedly depressed by pilocarpine. The rate is greatly slowed and the amplitude of the respiratory excursions diminished. The slight initial stimulation of the vasomotor center is followed by paralysis.

7. **Pilocarpine on the alimentary tract.**—Pilocarpine produces a marked, in fact violent, increase in the peristalses of the stomach and intestine. It stimulates at the point of union of the motor nerves and smooth muscle cells, picking out the motor mechanism apparently to the exclusion of the inhibitory mechanism. This action is easily demonstrated by rings of muscle from the stomach of a cold-

blooded animal. It is expressed also in the gripping muscular contractions with pain and by the occasional purging and vomiting noted after the excessive administration of pilocarpine.

8. Action of pilocarpine on the iris and the ciliary mechanism of the eye.—The constriction of the pupil is an obvious and easily

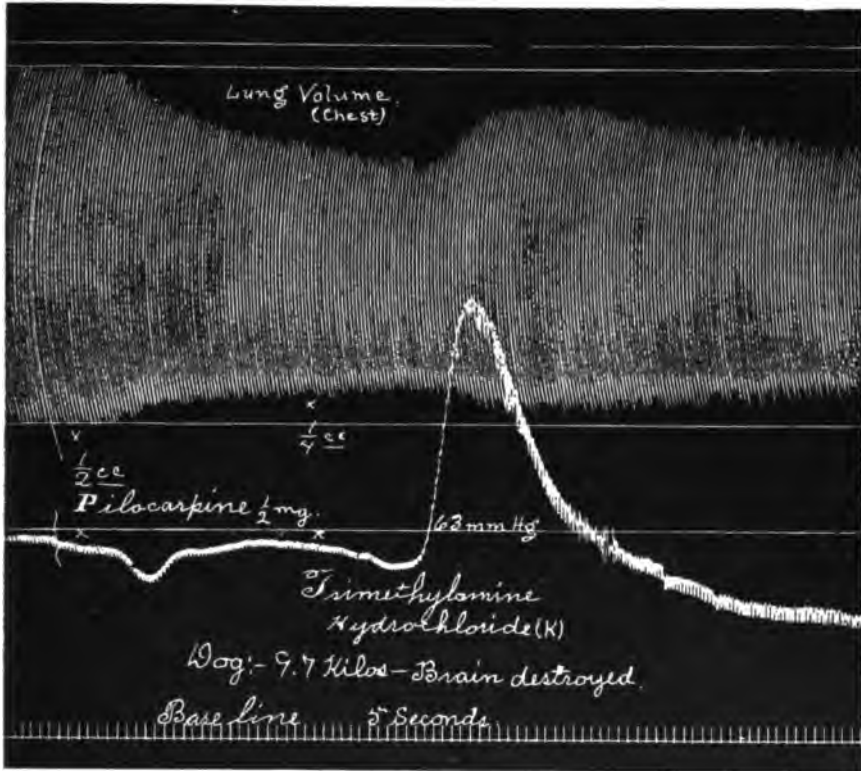


FIG. 33.—Influence of pilocarpine on the bronchial muscles, and on the blood-pressure. Trimethylamin hydrochloride produced the opposite result. The further details of the experiment are explained on the figure. From Jackson.

noted result associated with the symptoms of pilocarpine action. The accommodating mechanism is also stimulated to contraction. Reference to the discussion of the action of atropine, also of epinephrine, where a review is given of the normal physiological mechanism of the eye, will show that the contraction of the pupil depends upon a stimulating action of either some portion of the oculo-motor nerve or of the smooth muscle of the iris itself. Anderson¹ has especially

¹ Anderson, H. K.: *Journal of Physiology*, Vol. XXXIII., p. 414, 1905.

investigated the problem. By a series of exclusion experiments he has shown that pilocarpine produces an even stronger contraction of the iris after section of the oculo-motor nerve, as it does also after removal of the ciliary ganglia. In this last case the contraction is more prolonged than when the oculo-motor nerves are intact. One hundred and nineteen days after removal of the ganglia, when the short ciliary nerves are presumed to be degenerated, pilocarpine still produces contractions of the constrictor muscles of the iris. He came to the conclusion that pilocarpine can act on the sphincter muscle itself. It is admitted, however, on the basis of greater response with intact nerves, that pilocarpine acts also at the point of nerve endings. The accommodative spasm is explained in light of these experiments as a peripheral muscle and motor-nerve stimulating effect of pilocarpine.

IV.

Condensed Summary of the Pharmacological Action of Pilocarpine.

Pilocarpine and related alkaloids lead to marked stimulation of the peripheral motor structures. There is a striking increase in the amount of perspiration, saliva and other secretions of the alimentary and respiratory tracts. Pilocarpine has no direct physiological action on the mammary gland or on the kidney, but it increases the glycogenic functions of the liver. The nervous muscular mechanisms of the eye are sharply stimulated through action on the nerve terminations and on the constrictor muscle itself. The heart is slowed by an initial stimulation of the inhibitory mechanism at its terminations, an effect which is followed by final paralysis. In therapeutic doses medullary centers are slightly stimulated, in large doses paralyzed. The paralysis is most marked on the respiratory center and on the vasomotor center. In toxic doses heart muscle is weakened and the circulation depressed, the respiration is shallow, and edemic obstruction may take place in the lungs.

Pilocarpine is antagonized by atropine, which is an antidote.

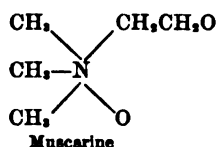
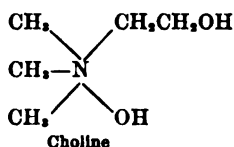
II. MUSCARINE.

I.

Historical and Chemical.

Muscarine is a very toxic alkaloid present in the poisonous mushroom, *Amanita muscarius*. Schmiedeberg has produced an artificial

muscarine by the oxidation of choline, to which it is closely related, having the formula $C_5H_{14}NO_3$. The chemical relationship between choline and muscarine is shown by the following structural formulæ:



II.

Outline of Pharmacological Action.

The action of muscarine is very similar to that of pilocarpine, though it is more strongly stimulative of parenchymal tissues. Its general effects are:

1. *A marked slowing of the heart by stimulation of vagus terminal endings.*
2. *Accommodation spasm, with constriction of the pupil of the eye.*
3. *A marked increase in gastric and intestinal peristalses.*

III.

Details of Pharmacological Action.

1. **Muscarine on the heart and circulatory system.**—The typical action of muscarine is illustrated by its influence on the heart. When muscarine is perfused through the frog heart or painted over the whole heart a marked slowing leading to complete standstill quickly ensues. The muscarine effect is not due to a paralysis of the contractile substance, since at any time direct stimulation of the ventricle of the heart leads to a contraction. The muscle tissue is irritable and contractile, but held in inhibition. This picture is further emphasized by the immediate recovery of contractions after painting the heart with atropine. The pause disappears and a perfectly normal rhythm ensues. It is evident that atropine and muscarine act upon the same structures, namely, the terminal fibers of the vagus in the heart tissue.

In certain animals, especially invertebrates which have well-developed cardiac nerves, there is a specific stimulation of the accelerator mechanism, in a way comparable to the stimulation of the inhibitory mechanism in most mammals. Muscarine is without marked effect

on cardiac tissue as such, hence does not influence the embryonic heart before the nervous connections are established. However, there is a slight direct effect on isolated ventricular muscle of the terrapin, a general increase in the amplitude of the contraction with a somewhat slower rate.

2. **On blood-pressure.**—The administration of muscarine leads to an enormous fall of blood-pressure, but these results are almost exclusively due to the cardiac inhibition as previously described. Upon the intravenous injection of muscarine there is as complete a cessation of heartbeat in the mammal as results from effective vagus stimulation. This action can be controlled by graded doses almost as completely as the vagus itself. This inhibition is removed by counter injection of atropine, under the antagonistic action of which the blood-pressure recovers.

3. **Muscarine on the glands and on the alimentary tract.**—Muscarine produces an increase in the secretion of salivary and other glands of the mouth and alimentary tract by a stimulation of the terminal secretory fibers at the same point acted upon by pilocarpine and apparently in the same way.

In a similar manner there is a marked increase in the peristalses of the stomach; in fact, of the entire intestinal tract. A 0.5-milligram dose of muscarine per kilo given to a cat or dog is sufficient to produce violent secretion of the salivary glands, and intense contractions of the stomach and intestine, with vomiting and purging.

4. **On the eye.**—Muscarine produces a constriction of the pupil and contraction of the muscles of the accommodating mechanism of the eye. These results are accomplished through stimulation of the endings of the oculo-motor nerve on the muscle fibers involved. The stimulation of the terminal fibers of the oculo-motor is more prolonged and enduring with muscarine than with pilocarpine, the toxic action of the latter tending to paralyze the mechanism.

III. PHYSOSTIGMINE, OR ESERINE.

I.

Historical and Chemical.

Physostigmine is derived from the seeds of the Calabar bean, *Physostigma venosum*, of the western portion of Africa. It has the chemical formula, $C_{15}H_{21}N_5O_2$. It was first isolated in 1864 by Jobst and Hesse.

II.

Outline of Pharmacological Action.

Physostigmine, like pilocarpine and muscarine, produces a profound stimulation of terminal nerve fibers, but with greater effect on the parenchymal tissue itself.

1. *Marked constriction of the pupil and accommodative spasm of the ciliary muscles of the eye.*

2. *A powerful stimulation of the muscular mechanism of the stomach, intestine, and the muscles of the urino-genital apparatus.*

3. *A stimulation of the cardiac inhibitory apparatus.*

4. *Initial slight stimulation, with deep depression of the function of the medullary centers, and to some extent of those of the spinal cord.*

III.

Details of Pharmacological Action.

1. **Physostigmine on the eye.**—The local ocular effects of physostigmine are demonstrated by dropping a one per cent. solution over the surface of the eye. After 20 to 30 minutes the pupil becomes constricted and the ciliary muscles sharply contracted, and the eye accommodated for near vision. This accommodative spasm lasts for several hours, three or more. The explanation of the physostigmine action is based on the view that the terminal fibers of the oculo-motor are sharply stimulated. If one stimulates the cervical sympathetic in the neck there occurs the normal complete dilation of the pupil, showing that this apparatus is not involved, i.e., not paralyzed by the action of the alkaloid. That the action is on the terminal fibers is shown by the fact that constriction takes place after operation, cutting the short ciliary nerves or removal of the ciliary ganglia. If degeneration of these peripheral fibers is allowed to take place, then the eserine effect is less marked or lost. It was formerly thought that physostigmine produced a direct stimulation of the muscles themselves.

Anderson, who has performed degeneration experiments on numerous animals, finds that physostigmine is not active on the iris after the peripheral nerves have degenerated. Acceptance of this observation tends to throw doubt on the current view that physostigmine stimulates smooth muscle in numerous other organs. He finds that physostigmine contractions return early in the regeneration of

these fibers, even before they become sensitive to electrical stimulation. All these facts point to localization of the action on the endings of the oculo-motor nerve. Heine has demonstrated by histological methods that the ciliary muscles of the eye and the muscles of the iris are actually contracted in eserine poisoning.

Physostigmine also contracts the striated muscles of the bird's eye, differing in this respect from the action of atropine, which does not paralyze striated nerve endings.

2. **Physostigmine on the circulatory apparatus.**—Intravenous administration of physostigmine produces an immediate fall of blood-pressure. If the dose be toxic the picture is similar to that upon the maximal stimulation of the vagus nerve. In the therapeutic dose there is a marked slowing of the heartbeat associated with intermediate periods of more complete cardiac inhibition. This effect is to be explained on the ground of marked vagus stimulation for the whole heart. Atropine removes the depressing action of physostigmine by counteracting its effect on the nerve endings. It would seem that little or no central stimulation occurs on those nervous centers regulating the circulatory apparatus. Carlson, however, has shown that the extra-cardiac ganglia of limulus are stimulated by relatively strong solutions of physostigmine.

The isolated vertebrate heart or the heart tested *in situ* always shows a pronounced slowing upon the administration or application of physostigmine. The physiological analysis of the results proves that this action is primarily due to pronounced stimulation of the terminal vagus fibers as in muscarine poisoning. There is this difference, namely, that atropine does not completely eliminate the eserine. Experiments on isolated strips of terrapin heart reveal the reason of this failure of complete atropine antagonism. Strips subjected to physostigmine solutions, .01 to .02 per cent. in physiological saline, show a slight slowing with a pronounced increase in the amplitude of contraction. The increase of amplitude is interpreted to mean a direct muscular stimulation. The slowing is not so easily explained. One may assume that the terminal inhibitory fibers in this isolated muscle are stimulated somewhat slowing the rate, but the stimulation is not pronounced enough to overcome the direct effect on the amplitude of the contractions. This we have checked on strips from tested atropinized hearts and find that now the increase in amplitude of contractions is greater and that the rate is often, though not always accelerated.

3. **Physostigmine on striped muscle.**—Physostigmine differs from

other members of this series in that it stimulates skeletal muscle. The effect of the drug apparently falls both on the motor end plates and on the striated muscle substance. The former deduction is proven by the fact that sub-minimal stimuli for normal motor nerves become effective after the administration of physostigmine.

Physostigmine will increase the irritability of the motor end plate sufficiently to overcome or antagonize the less profound paralyses produced by curare. Pal has shown that a curarized animal, in which the voluntary muscles were no longer active to nerve stimulation, will recover the motor control after intravenous injection of physostigmine. He considers physostigmine a true antagonist and antidote to curare. Skeletal muscle is set into fibrillar contraction by stronger solutions of physostigmine.

4. **Physostigmine on the muscles of the stomach and intestines.**—The peristalsis of the stomach is markedly increased by physostigmine in a manner similar to that of pilocarpine and muscarine. Intestinal peristalsis is also increased. These effects are accomplished through stimulation of the terminations of the vagus nerve, i.e., the terminal neurone in the vagus path. Eserine produces more pronounced contraction in these organs because it also directly stimulates the unstriated muscle. The gall bladder and its sphincter strongly contract. In fact, all organs possessing the unstriated muscle are set into a greater or less degree of contraction by eserine. The spleen, the urino-genital apparatus, including the uterus, and the muscles of the small arteries are all involved.

Atropine is only partially antagonistic to this physostigmine effect. It does not eliminate the direct muscular action, only antagonizing that factor due to the stimulation of the nerve ends, but not counter-acting the blood-vessel effects nor the striated muscle stimulations.

5. **On the central nervous system.**—The influence of physostigmine on the medullary centers controlling the circulation is wholly insignificant, but the action of physostigmine on the respiratory center is of special importance. Therapeutic doses have been described as leading to initial acceleration of respiration, though in laboratory experiments on mammals this acceleration is slight and quickly passes into a slow respiratory rate with diminished amplitude and final complete inhibition. The respiratory pause is not due to the interference with the motor nerve endings, since, as has already been stated, these are stimulated. Section of the vagus nerve does not eliminate the effect, hence we must assume that the toxic influence is on the respiratory center itself. If, in a mammal during physostig-

mine respiratory pause, atropine be injected intravenously, there is ultimate respiratory recovery. The first influence of the atropine is of course to release the heart from the vagus control, which mechanism is under stimulation by physostigmine. Then, after a variable interval, amounting in one published illustration¹ to 30 seconds, there is a slow, gradual recovery of respiratory rate and amplitude. One must explain this striking antagonism of atropine for physostigmine as due to the fact that atropine is much more profoundly stimulative in its primary action on the respiratory center. The toxic stage of both drugs leads to paralysis of this nervous mechanism. A toxic dose of physostigmine is small and produces cessation of respiratory movements long before elimination of function of the circulatory apparatus. In ordinary toxic doses the cause of death is respiratory failure with asphyxiation.

IV.

Condensed Summary of Action.

Physostigmine has a pronounced stimulating effect on practically all motor nerve terminations—the salivary glands, gastric glands, lachrymal glands; the muscular apparatus of the eye, of the stomach and intestine, of the bladder and uterus, and of the bronchial tubes. It stimulates the nerve terminations in skeletal motor nerves, antagonizing curare. Eserine also stimulates practically all the active parenchymatous tissues, such as the glands, the heart muscle, skeletal muscle, and all smooth muscle tissues, with the exception of those of the eye. It has an ultimate paralytic effect on the nerve centers of the medulla the respiratory center being especially sensitive. The action of physostigmine is antagonized by atropine on all nerve structures which are primarily stimulated by physostigmine, but its terminal action on the peripheral tissues is not so antagonized.

¹ Greene, Chas. W.: *Experimental Pharmacology*, p. 46, Fig. 2, Philadelphia, 1909.

COMPARISON OF THE PILOCARPINE GROUP.

	Central nervous system	Nerve endings in glands	Nerve endings in smooth muscle.	Cardiac vagus endings.	Skeletal muscle endings.	Direct action on terminal tissues.
Pilocarpine.	Depressing to axial nerve centers.	Violently stimulates in all glands except kidney and mammary.	Stimulates alimentary, urino-genital system, and eye.	Stimulates.	No effect.	Slight but questionable.
Physostigmine.	Slight initial stimulation and early and profound paralysis of axial centers.	Stimulates.	Violently stimulates all structures.	Strongly stimulates.	Stimulates.	Stimulates but questionable as to the eye.
Muscarine.	Stimulation followed by depression.	Stimulates.	Vigorous stimulation.	Violent stimulation.	Paralysis.	Little or none.
Atropine.	Vigorous stimulation and toxic paralysis.	Simple paralysis.	Paralysis.	Paralysis, except blood-vessels and inhibitory nerves of alimentary canal.	No effect.	No effect.

CHAPTER XIV.

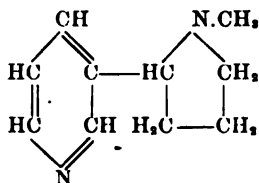
THE NICOTINE SERIES.

I.

Historical and Chemical.

Tobacco, *Nicotiana tabacum*, possesses an alkaloid, which has certain characteristic influences on the reactions of the body, to which the widespread use of tobacco is to be attributed. Tobacco was introduced into general use among Europeans following the discovery of America. Lord Raleigh, who was impressed by the Indian custom, brought home tobacco and taught the English court the Indian method of smoking it. At the present time the use of tobacco is widespread, and is chiefly limited to smoking and chewing. The latter method results in the swallowing of small quantities of the juices of tobacco with the saliva, while the former results in absorption of nicotine and related chemical derivatives from the smoke inhaled.

Chemically nicotine is a pyridine of the following structural formula as given by Schmiedeberg:



When heated, as in cigar smoking, the nicotine is partially broken down, forming pyridine and pyridine compounds.

Lobelia inflata possesses an alkaloid, lobeline, with the chemical formula, $C_{15}H_{23}NO_2$, which has a physiological action similar to that of nicotine. *Duboisia Hopwoodii* possesses an alkaloid, piturine, $C_{12}H_{16}N_2$. This alkaloid has effects identical with nicotine, according to Langley and Dickinson.

The water hemlock, *Conium maculatum*, contains a series of alkaloids, which have reactions in the body somewhat similar to nicotine. Of these coniine is the most important.

II.

Outline of Pharmacological Action.

1. *Nicotine produces a primary but mild stimulation of the nervous system at all points, followed by a marked depression.*

2. *It is specific in its action upon the pre-ganglionic synapses of the autonomic system, at first mildly stimulating, but later producing a profound and prolonged paralysis.*

3. *Cardiac muscular tissue is at first strongly stimulated, then later depressed. Other muscular tissues, the smooth muscle, and skeletal muscle, are similarly though less strongly affected.*

III.

Details of Pharmacological Symptoms.

Nicotine is a drug which is strikingly disturbing to the normal functions of the body. When it is used for the first time and in semi-toxic amount the symptoms indicate a profound general stimulation of all parts of the body. There is increased respiration, a general rise of blood-pressure, vasomotor constriction, a slow heart in the incipient stage, but a rapid and irregular heart in the advanced stage. There is nausea with vomiting, very often accompanied by increased peristalsis of the alimentary tract and purging. Excessive doses may cause death, which is produced through paralysis of the respiratory muscles and of the central nervous system.

1. **On the central nervous system.**—Nicotine stimulates the entire central nervous system, apparently more strongly from above downward. This stimulation is slight and transient, giving way to a depressed or sedative condition.

2. **On the cerebral cortex and medulla.**—Beneficial action of nicotine on the cortex has not been demonstrated in so far as the ability to do psychic work is concerned. Under conditions of mental disturbance and hyperirritability nicotine is said to contribute to a feeling of comfort and quiet, i.e., is soothing to an overwrought nervous mechanism. This effect is undoubtedly an expression of the second stage in the responses of the body to the alkaloid.

On the basal centers of the nervous system, especially of the medulla, the initial stimulating action of nicotine is more pronounced. This is shown partly through the great automatic regulative centers controlling the action of respiration, the circulation, the alimentary,

and glandular systems. The respiratory center is stimulated to an increased respiratory rhythm and amplitude. In the more advanced stages this effect gives way to one of depression. The cardiac regulative centers, both inhibitory and accelerator, are likewise rendered more sensitive. This leads to a slowing of the heart through the central stimulation, since the inhibitory mechanism is preponderant. After the action of nicotine becomes more intense, the accelerator mechanism is more profoundly stimulated, hence there will be periods of cardiac acceleration approaching palpitation. The vasomotor center is at first sharply stimulated, leading to a marked peripheral constriction of the arterioles. Later this gives way to vasomotor paralysis. The medullary nerve centers controlling the sweat glands of the skin, the salivary glands, also probably the gastric and pancreatic glands, are at first stimulated, then later depressed.

3. **The spinal cord.**—The nervous mechanisms of the spinal cord are not so profoundly involved as those of the medulla. However, the reflex centers of the cord are rendered more sensitive to the ordinary inflow of stimuli, hence give more profound discharges than normal. This condition is quickly followed by one of obvious depression, which in the toxic stage may result in motor paralysis.

4. **Nicotine action on the peripheral ganglia.**—The specific action of nicotine falls not upon the central nervous axis, but upon the peripheral ganglia of the autonomic nervous system. Here, too, nicotine produces a passing stimulation, but followed by a marked and quick depression, with complete elimination of function. This specific action takes place at the union between the pre- and post-ganglionic neurones.

Schmiedeberg was the first to properly locate the characteristic specific action of nicotine, proving the same by its influence on the cardiac inhibitory mechanism. He showed by a skillful series of experiments that the elimination of the vagus control over the heart was due to the loss of function in the cardiac ganglia. The stimulation of the vagus nerves in the neck failed to produce an inhibition of the heart at a time when stimulation of the ganglia of the heart at the sinus produced inhibition. It was evident that such an experimental result could only be obtained by a block of the nerve impulse in the cardiac ganglia.

This point of specific action of nicotine has been proven through later work to be general for all the autonomic mechanisms. Langley and his pupils have demonstrated this general law, and by turning the fact about and using it as a means of interpretation, have been

able to very greatly widen our physiological knowledge of the whole nerve complex of the so-called sympathetic system. The changes of function produced by nicotine on the various special motor organs are largely dependent upon the action of nicotine on the peripheral sympathetic ganglia. The usual delicate and well-balanced normal physiological responses become blunted or impossible when the nerve



FIG. 34.—Effects of nicotine on the contractions of the isolated sinus-auricle strip, terrapin. Between the arrows the preparation was bathed in .01 per cent. nicotine. A 70 second interval between the two parts of the record. Note both the tonic and the fundamental contractions are strongly stimulated, the tonic contractions at the beginning of the nicotine action, the fundamental contractions throughout. Time in seconds. New tracing by Williams.

control is eliminated by the nicotine blocking of nerve paths through the peripheral ganglia.

5. **The action of nicotine on the circulatory system.**—A physiological mechanism so complicated as the circulatory apparatus must of necessity be profoundly influenced by a drug which has widely distributed reactions in the human body. So it is with nicotine. This alkaloid causes marked changes at least at four fundamental points in the circulatory apparatus, namely, on the cardiac muscle itself, the heart's local nervous mechanisms, the medullary centers for the heart, and on the vasomotor nervous complex. The resultant activity of the circulatory complex produced by nicotine shows itself of course in changes in the blood-pressure, and pulse rate and pressure. A very weak dose of nicotine produces a rise of blood-pressure. If the nicotine action becomes stronger, as with a medium dose, this pressure remains up; in fact, continues to rise. Only in the toxic stage does the pressure fall and finally become *nil* at death. The components entering into and producing this rise of pressure are discussed more fully below, but the condensed statement is shown in the following table:

ACTION OF NICOTINE ON THE CIRCULATION.

	Dose.		
	Weak.	Medium.	Toxic.
Blood-pressure.....	rise	rise	fall
Heart rate.....	slow	rapid	{ slow and failing less
Heart amplitude.....	increased	greater	—
Vagus control.....	{ strongly increased }	{ decreased and lost }	{ decreased and lost }
Accelerator control.....	increased	increased	—
Vasomotors.....	increased	decreased	lost

6. The action of nicotine on cardiac muscle.—Cardiac muscle responds very sharply to the presence of nicotine, both by a change of rate and of amplitude, i.e., force of the contraction. Both these factors are increased under the stimulating action of therapeutic quantities of nicotine. The point can be proven readily by studies on isolated strips of cardiac muscle and by the reactions of isolated hearts, both mammalian or warm-blooded and the various cold-blooded hearts. Strips of ventricular muscle, when surrounded by physiological saline containing approximately .001 to .002 per cent. of nicotine show an increase of amplitude amounting to from 10 to 20 per cent. and an acceleration of the rate which is more or less variable. The perfused frog's heart shows comparable results.

The most striking illustration of this influence is found when the isolated mammalian heart is perfused with physiological solutions containing nicotine, as shown in Figure 35. Often the amplitude of the contractions of the heart is doubled and the rate strongly accelerated. Undoubtedly a similar cardiac muscular effect is produced on the heart in its normal relations in the body. The late and relatively toxic actions of nicotine are depressant for cardiac muscle. This factor appears in the after effects in those experiments in which there is a maximum of primary stimulation.

7. The local nervous apparatus of the heart.—The peripheral nervous reactions to nicotine are best demonstrated by perfusions either on isolated organs or in blood-pressure studies. If one follows Schmiedeberg's technique, the results of which have already been given, he will note that the heart is at first slightly slowed for a few minutes, probably due to the local stimulation of the nerve

cells of the cardiac ganglia. This stage, however, quickly passes. If now the vagus nerve, or the vago-sympathetic of the frog be stimulated in the neck, there is no longer an inhibition of the heart. In the frog, in fact, there is generally an acceleration. Direct stimulation of the sinus still produces inhibition, the observational fact on which Schmiedeberg reached his deduction that the pre-ganglionic nerve endings are blocked in the sinus ganglia. The fact that the ganglionic endings of the accelerator nerves in the frog are located central to

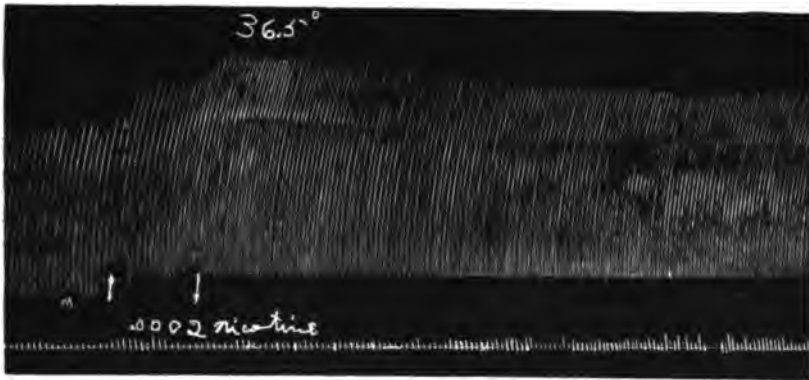


FIG. 35.—Nicotine, 0.0002 per cent. in blood-Ringer's solution, on the isolated heart of the cat. Temperature and perfusion fluid constant. A later experiment with .0005 per cent. showed a more pronounced increase in the amplitude followed by a stage of depression from which recovery was very gradual. Rate before perfusion 56, immediately after, 84. New tracing by Boutwell and Peeler.

the point stimulated explains the acceleration observed in that animal. If one would dissect back of the stellate ganglion, in the frog to the white ramus from the third spinal nerve and apply an electrical stimulus, the acceleration observed on stimulation of the vago-sympathetic trunk will not occur. The nicotine has evidently poisoned the pre-ganglionic endings in the accelerator path just as effectively as in the inhibitory path.

Emphasis has just been laid on the systemic effects that come from elimination of the coördinative nervous mechanisms. No better organ could be used in presenting the detrimental effects of the toxic alkaloïds than this one of the action of nicotine on the cardiac regulative nerves. Certainly the coördinative control of the heart is one of the most fundamental factors in normal physiology. The elimination of this control, therefore, is obviously profoundly injurious.

8. The vasomotor system.—Notwithstanding the cardiac slowing observed, the blood-pressure generally rises when nicotine is injected

intravenously. This rise of blood-pressure is in no small part to be attributed to an increased tone of the peripheral blood-vessels. The central effects have already been mentioned, but there are also undoubtedly peripheral actions, since vasoconstrictions occur in organs isolated from the central nervous system. Occasionally there is some vasodilation, instead of vasoconstriction, suggestive of stimulation of the vasodilator mechanism.

When the tonic action from the cardiac inhibitory mechanism is eliminated, the blood-pressure may rise quite decidedly, largely from persistent vascular contractions. The blood-vessels dilate in the toxic stage.

9. **On the glandular apparatus.**—The peripheral glands show an increased secretion upon the administration of nicotine. This is due to the central action of the drug on the medullary nervous mechanism. In the larger doses the peripheral ganglia are specifically poisoned and the reflex secretion correspondingly suppressed. It is not clear to what extent nicotine acts on the gland tissue as such.

10. **The action of nicotine on the eye.**—Nicotine paralyzes the nervous mechanisms of the eye. In fact, one of the simplest methods of demonstrating the specific nerve action of nicotine in laboratory use for many years, thanks to the researches of Langley, is that of bathing the cervical nerve and the superior cervical ganglion with 0.5 per cent. nicotine. Bathing the nerve trunk does not interfere with the passage of a nerve impulse. The function of this ganglion is blocked by the specific nicotine poisoning of the synapses and there is a failure of the usual dilation of the pupil upon cervical stimulation.

The oculo-motor nerve has its pre-ganglionic unions in the ciliary ganglion. Nicotine poisons at this point too, hence tends to eliminate the conduction of the nerve whose function is to produce constriction of the pupil and an act of near accommodation, both processes vital to the adaptations of the eye to delicate vision. The diagrammatic relations of the nervous apparatus involved are illustrated in Figure 26, under the chapter on atropine. The resultant general effects of nicotine vary somewhat in different animals, but in man there is usually some degree of contraction of the pupil.

11. **Nicotine on the alimentary canal.**—The complicated physiological control of the alimentary canal has been reviewed in some detail in the chapter on morphine. In order to understand the action of nicotine one should keep in mind that complex interrelation

of neurones involved in coördination of the function of the *vagus* motor fibers, the sympathetic inhibitory fibers, also the relationships of the plexuses of Meissner and Auerbach. Much of our information has been obtained by studies on isolated portions of the alimentary tract, especially the contributions of Magnus.

Nicotine, in the general circulation, causes as one of its striking symptoms, violent peristalses of the alimentary canal. This symptom is noticed and often spoken of by the social users of tobacco. However, it is a symptom which comes in the more pronounced stage of nicotine intoxication, i.e., upon the smoking of strong cigars. As a matter of fact, the very first and mildest influence of nicotine on the alimentary canal is a quieting or inhibitive phenomenon. This is due to the influence of the alkaloid on the sympathetic or inhibitive fibers, the incipient nerve stimulative stage that has been noted in several previous connections. This stage is soon passed over, being followed by specific toxic elimination of the sympathetic endings in the ganglia of the walls of the stomach and intestine. The elimination of the pre-ganglionic neurones sets the Auerbach's plexus of the alimentary canal free, which, according to Magnus, controls the local peristalses of the isolated organ. It is open to question, yet the probabilities are that nicotine acts as stimulative to the nerve cells of the plexus of Auerbach. The alternative to this view, however, would explain the increased peristaltic movements of isolated preparations by a direct influence on the muscular tissue. Even large doses of nicotine do not paralyze the contractions of isolated portions of the intestine. Magnus found that if atropine was combined with nicotine, then paralysis occurred, a result which would tend to the view that the nicotine alone acted on the nervous rather than the muscular tissue.

12. **Excretion of nicotine.**—Nicotine is largely excreted from the body through the kidney. However, there is a slight amount of excretion through general glands, such as the sweat glands, salivary glands, etc. Apparently there is some fixation and oxidation of nicotine by the tissues, though this is probably slight.

IV.

The Nicotine Habit.

The social use of tobacco is one of the most widespread of all drug habits, tobacco at the present time being used in smoking, chewing, and taken in powder form as snuff. It has little place in prac-

tical therapeutics, yet from the standpoint of experimental pharmacology and of toxicology it is very important.

It is very difficult to secure an accurate and scientific estimate of the effects on the body of the constant use of tobacco. A great deal has been written and said, some advocating strongly that no appreciable effects follow the social use of tobacco, others with an equal vehemence attributing extensive and profound disturbances to its presence. The scientific observations depend, for the most part, on acute experiments such as have been related in the preceding pages. Obviously a summary of these pages shows that the alkaloid nicotine either directly or indirectly produces variations in the function of practically all parts of the body. Stated generally this variation is a mild incipient acceleration of functional activity followed by a general depression and toxicity in the more pronounced stages of its influence. The picture is complicated by selective toxicity to the widely distributed autonomic mechanisms. One must assume that repeated use of the drug produces the same cycle of changes, though their relative intensity varies greatly in that the body only slowly regains its normal condition after it has once been subjected to nicotine. All succeeding doses, i.e., smokes, etc., proceed from a very much changed norm. Then, too, a marked tolerance is acquired by the body as an organism.

A single use, say the first smoke of tobacco, will leave the body in a condition somewhat depressed below its normal average functional alertness. This depression falls upon the nervous system, both central and peripheral, on the heart, blood-vessels, glands, alimentary canal, and muscles. Repeated use is followed by similar, but more accentuated depression. This is just the foundation for that condition of general body sensation which drives an individual to continued use of any agent which runs the cycle of initial stimulation and after depression, typical of nicotine. These depressed sensations and general body feelings urge to repetition of the earlier experience. When the use of the drug is mild, what is generally considered as moderate, then the driving sensations are less vigorous. If the indulgence is extreme in any instance the disturbance of mental poise and well-being is correspondingly great. The individual takes tobacco, therefore, in order to produce and maintain that incipient stimulative stage. He is driven to continued repetition by the after depressions which characterize the action of tobacco in every form.

Any stimulative agent acts like a whip to the physiological mechanisms of the body. If those mechanisms be delicately poised and

high strung, then the whip leads to nervousness and incoördination in the early phases of its action and to inevitable fatigue and exhaustion later. Repetition of the stimulus, in the long run, leads to an average physiological state which is far below the average normal for the individual before the use of the drug. One is led to suspect that herein lies the evil in the case. While there is no vital lesion resulting from the use of tobacco there is a diminution of the delicacy

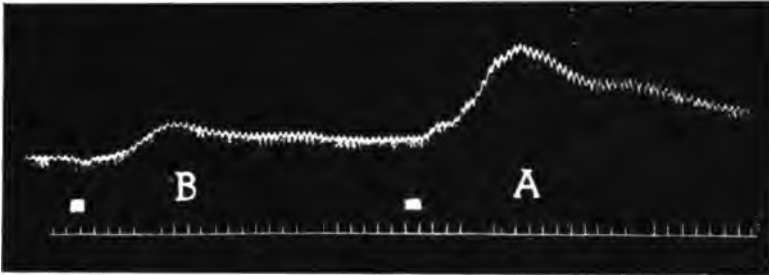


FIG. 36.—Blood-pressure in the decerebrate cat. The effects of the injection of liver extracts, A from a normal rabbit, B, from a nicotine tolerant rabbit. The extracts were made from equal parts of pulverized and dried liver, and each was incubated with 0.01 gram of nicotine for two hours and thirty minutes. Time—5 seconds. From Dixon and Lee.

of sensibility, a reduction of physiological ability, a slight but general lowering of the energy and endurance of the body.

Tolerance.—It is a well-known fact that individuals respond less strongly to successive doses of nicotine. While the first cigar may produce acute symptoms of nicotine poisoning the individual soon acquires the ability to smoke, not only one, but several without the extreme symptoms. Dixon and Lee¹ have lately attacked this problem. By the method of repeated doses of nicotine, extending through several weeks' time, they were able to secure animals of marked tolerance. Proceeding on the theory that "nicotine tolerance is due to the destruction of the alkaloid by the tissues" they made liver extracts of tolerant animals with non-tolerants for controls. These extracts were each mixed with a definite quantity of nicotine, allowed to incubate for two and one-half hours, then were estimated for nicotine content by the physiological method of blood-pressure.

Dixon and Lee say, "These experiments show that a certain small degree of tolerance can be obtained to nicotine, and that this is brought about by the destruction of the alkaloid. The destruction goes on very

¹ Dixon, W. E., and Lee, W. E.: *Quarterly Jour. of Experimental Physiology*, Vol. V., pp. 373-383, 1912.

slowly, and it can never be accelerated to such a degree that an injection of a poisonous dose of nicotine into the circulation of an animal will lose any large amount of its effect. If the nicotine reaches the circulation slowly and in minute quantities it may be dealt with by the tissues, and this is the condition which we may assume obtains during tobacco smoking." These observations indicate that such nicotine tolerance as is acquired depends upon the development of an oxidizing enzyme by the tolerant individual.

CHAPTER XV.

THE CONIINE, SPARTEINE GROUP.

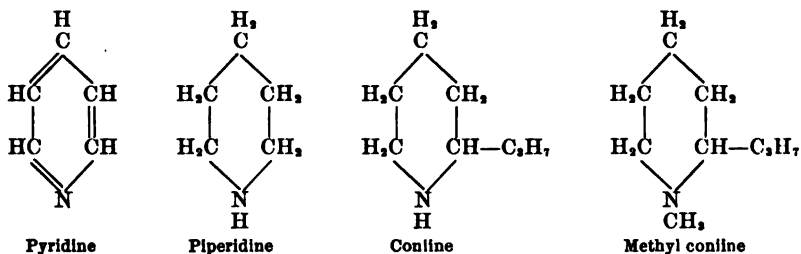
The alkaloids of this group form an intermediate series between nicotine on one hand and curare on the other. The most important members of the series are coniine, lobeline, gelseminine, and sparteine. The most important member is coniine, which may be taken as illustrating the actions of the other members. The chief difference is that of intensity and relative degree of toxic action.

I. CONIINE.

I.

Historical and Chemical.

The poisonous water hemlock, *Conium maculatum*, yields both from its roots and the stem the alkaloid coniine, together with methyl coniine, and conhydrine. Coniine is a piperidine compound and is interesting in that it was the first vegetable compound produced synthetically in the chemical laboratory, Hofmann in 1881. Methyl coniine differs from coniine by the substitution of methyl for the hydrogen attached to the nitrogen. Coniine has the chemical formula, $C_8H_{17}N$. The chemical relationships are indicated by the following formulæ:



II.

Outline of Pharmacological Action.

1. *Coniine produces a very mild initial stimulation of the central nervous system, followed by pronounced depression and paralysis.*

2. *It is toxic to peripheral nerve ganglia, acting similar to nicotine.*
3. *Coniine is toxic to motor nerve endings of striated muscle, resembling curare.*

III.

Details of Pharmacological Action.

1. **On the central nervous system.**—Coniine, like nicotine, produces some stimulation of the central nervous system, but this effect is so slight and the depressing action so strong that the stimulating factor becomes insignificant. The symptoms on man are characterized by depression. Following a therapeutic dose there is drowsiness, irregularity of respiration, unsteadiness of gait, slight dilation of the pupil, secretion of saliva with a tendency to nausea, and sometimes vomiting.

In toxic dose coniine, especially in the impure form, is characterized by the production of a general paralysis, which involves the voluntary muscle system. The paralysis is progressive, ending finally in loss of respiratory movements. Schmiedeberg indicates that the toxic cycle is quickly passed and that death follows in from three to four hours. As an illustration of the toxic action we have Plato's classical description of the death of Socrates under the administration of the poison cup, which, judging from the symptoms alone, has been attributed to the poison hemlock.

2. **On the autonomic nervous system.**—Coniine, like nicotine, poisons the peripheral nerve ganglia. It is this which chiefly leads to disturbances of the normal physiological reactions of the peripheral tissue innervated through the autonomic system. There is some indication of an initial stimulation of these ganglia, though this stage is very slight and evanescent. The main picture is that of tissue paralysis. However, it takes a larger dose of coniine to produce this poisonous effect than of nicotine, about, in the ratio of 1 to 20.

3. **On the voluntary motor nerve endings.**—Coniine has a paralyzing effect on voluntary nerve endings, similar in kind to that of curare.

When coniine is administered hypodermically to the frog the animal soon loses its usual erect position, lies flat on the supporting surface with the legs more or less extended. It shows, in the toxic stages, some muscular twitching and irregular muscular reactions, which have some superficial resemblance to muscular cramps. However, this effect is primarily due to partial paralysis of the nerve endings

which eliminates the coördinative nervous control over the voluntary muscles. The presence of the muscular twitchings depends upon some central nervous change of an exciting nature, supposedly in the spinal cord. When complete paralysis of the motor endings takes place the twitchings cease. Respiration necessarily ceases, hence asphyxiation and death follow.

4. On the circulatory apparatus.—The action of coniine on the circulatory apparatus is primarily due to its interference with the nervous mechanism. A transient rise of blood-pressure has been observed. This is attributable to a peripheral vasoconstriction, which is explained by some as of peripheral origin, possibly an expression



FIG. 37.—Coniine on the contractions of ventricular muscle, terrapin. Between the points "on" and "off" the muscle was bathed with .006 per cent. coniine. Time in seconds.

of the initial stimulation of peripheral ganglia in the vasomotor nerve mechanism. In the later stages the blood-vessels are dilated and the pressure falls. This is due to paralysis at the same points which receive the initial stimulation, i.e., the peripheral ganglia of the vasomotor nerves. This paralysis eliminates the tonic vasomotor action.

The heart is little affected by coniine, in so far as the muscle is concerned, though its nervous mechanism is deranged. At first the heart beats somewhat slower from the initial stimulation of the vagus, but as paralysis of the cardiac ganglia quickly ensues the tonic vagus control is eliminated and acceleration occurs. In those lower animals, which have no vagus tone, this phenomenon is not observed.

5. On the respiratory movements.—While the respiration under the influence of coniine shows some slight acceleration at first, the main picture is that of weakness and irregularity, the respiration becomes slow and the type of respiration shallow and irregular. In the toxic stage respiratory action is the first to disappear and death results from asphyxiation.

Some difference of opinion exists in the literature as to whether

respiratory paralysis is primarily central or peripheral. The curare-like poisoning of the motor nerve endings is thought by many to be sufficient to account for the stopping of respiration.

6. **The excretion of coniine.**—This alkaloid is excreted in the urine in part unchanged. Coniine rather readily breaks down and it is probable that a certain proportion of the drug may be decomposed in the tissues. The excretion and decomposition is rapid, hence in coniine poisoning artificial respiration may ward off asphyxiation until recovery becomes possible.

II. PYRIDINE AND PIPERIDINE.

The action of pyridine and piperidine is similar to that of coniine, though very much weaker and less toxic. The chief action of the simpler compound, pyridine, is that of depression of the irritability of the nervous system. It shows little peripheral toxicity for the ganglionic cells.

III. LOBELINE.

Lobelia inflata yields an alkaloid, lobeline, $C_{18}H_{23}NO_2$. Edmunds has described the action of lobeline as very similar, if not identical with that of nicotine.

IV. GELSEMININE.

Gelsemium sempervirens has yielded the alkaloids, gelsemine and gelseminine. The former alkaloid is described as producing strychnine-like effects, especially on the frog. Gelseminine produces symptoms very different from gelsemine and resembling the effects of coniine which have just been described.

Gelseminine has a greater depressant action on the responses of the central nervous system than coniine. This influences the centers of the medulla and chiefly the respiratory center, thus leading to respiratory paralysis and death.

Gelseminine, or some preparation of gelsemium, is employed rather widely to produce mydriasis. When drops are applied directly to the eye there is dilation of the pupil and loss of the power of accommodation. These phenomena are probably due in this case to paralysis of the nerve terminations in the muscles of the eye.

On the heart gelseminine produces elimination of the function of the vagus, in this case by an early nicotine-like action on the cardiac

ganglia, Cushny,¹ and by a later atropine-like toxicity to the vagus terminations on the cardiac muscle.

V. SPARTEINE.

Sparteine is a liquid alkaloid, derived from the broom plant, *Cytisus scoparius*.

Sparteine has a more toxic peripheral action and a less vigorous action on the central nervous system than other members of this series. In this regard it most closely resembles curare. Its fatal effects are due chiefly to the motor paralysis, especially of the nerves of the respiratory apparatus.

On blood-pressure sparteine has a somewhat depressing effect. This influence is primarily due to the lowering of the vitality of the heart through toxicity on cardiac muscle, depression which is accentuated by a slight initial vagus stimulation.

¹ Cushny, Arthur R.: "Die wirksamen Bestandtheile des *Gelsemium semper-virens*," *Arch. f. Path. u. Pharm.*, Vol. XXXI, pp. 49-68, 1893.

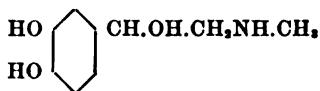
CHAPTER XVI.

EPINEPHRINE.

I.

Historical and Chemical.

The internal secretion of the epinephros, epinephrine or adrenaline, possesses the formula, according to Aldrich, $C_9H_{13}NO_3$. It is chemically an amino alcohol with a pyrocatechin base as follows:



This active material is elaborated in the animal body by the medulla of the suprarenal gland. That the suprarenal glands contain an active principle was first demonstrated by Oliver and Schaefer¹ in 1895. They worked with the extracts of the gland itself. Abel² was the first to isolate the active principle which he called epinephrine, and assigned the constitutional formula, $C_{10}H_{11}NO_3 \cdot \frac{1}{2}H_2O$. Takamine also isolated the active principle, calling it adrenaline, and perfected the methods for producing the material on a commercial basis. Folin has perfected a colorimetric chemical test for epinephrine accurate to 1 in 3,000,000 parts. The test rests on a quantitative application of the blue color reaction between adrenaline and phosphotungstic acid, compared in a colorimeter against a standard color solution. Many other glands of the body produce a physiologically active principle, which is given off to the blood or lymph. But the type of reaction of adrenaline is closely approximated to that of certain of the plant alkaloids that have previously been described, in that its action is specifically on the peripheral nerve endings.

II.

Outline of Pharmacological Action.

1. *Marked stimulation of sympathetic nerve endings of all types. The most striking of these groups are:*

¹ Oliver and Schaefer: *Journal of Physiology*, Vol. XVIII., pp. 230-277, 1895.

² Abel, J. J.: *Johns Hopkins Hosp. Bull.*, Vol. IX., p. 215, 1898; Vol. XII., p. 240, 1901.

2. *Vasoconstriction in most organs of the body, especially in the visceral regions.*

3. *Acceleration of the heart and stimulation of accelerator endings, complicated by*

4. *A secondary medullary stimulation of the vagus center.*

5. *Stimulation of the sympathetic nerve endings of the salivary and lachrymal glands.*

6. *Inhibition of physiological activities where the sympathetic furnishes inhibitory fibers, most pronounced in the gastric, intestinal, and uro-genital tracts.*

7. *Dilation of the pupil.*

8. *Glycosuria.*

III.

Details of Pharmacological Action.

1. **Action on the nervous system.**—Epinephrine is specific in its stimulative action on the terminal fibers of mechanisms of the sympathetic system in the various tissues. Hence the chief changes in the function of the body which are accomplished by this drug are those which involve reactions of the tissues controlled by the sympathetic nerves.

There is some slight acceleration of reaction of the basic centers of the central nervous system, particularly of the centers of the medulla. Of these, the only ones of special importance are the respiratory and the cardiac inhibitory centers. The slowing of the heart observed on adrenaline injection is generally attributed to stimulation of the medullary inhibitory center. However, in experimental procedures in which the blood-pressure is prevented from rising above the normal, this slowing is slight or absent. This fact bears the interpretation that the slowing of the heart is a secondary effect, produced by the increase in vagus tone, because of the marked general rise of blood-pressure.

2. **Epinephrine on blood-pressure—vasoconstriction.**—The intravenous injection of adrenaline into the circulation produces an enormous rise of blood-pressure, an effect first described by Oliver and Schaefer, who experimented with extracts of the gland itself several years prior to the chemical isolation of the active principle. With maximal doses the blood-pressure may rise from 100 to 150 per cent. The blood-pressure remains high for a few moments, then slowly declines to approximately the original pressure. A characteristic of the picture is its short duration, Figure 42.

The tremendous rise of pressure is due to a marked arterial constriction, which takes place, especially, in the visceral organs, such as the alimentary canal, spleen, kidney, also in the general systemic vessels. When, for example, either the kidney or the intestine is placed in an oncometer and adrenaline injected into the circulation, the volume sharply decreases and the organ remains under its normal size, even at a time when the blood-pressure is at its maximum.

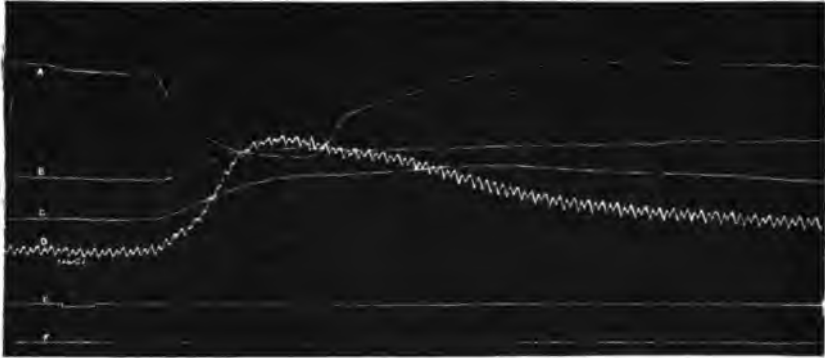


FIG. 38.—Intravenous injection of 0.1 gram of suprarenal of the calf. Dog with the vagi cut; the brachial plexus cut on the right side only. A, kidney volume; B, volume of the right arm; C, volume of the left arm; D, carotid blood-pressure; E, blood-pressure. The time of the injection as marked. From Oliver and Schaefer

Meltzer¹ has shown that the duration of the vasoconstriction is dependent upon the maintenance of the normal relations of the sympathetic nerves. For example, if the cervical nerve of the rabbit is previously cut, then adrenaline produces a slower, longer, and stronger constriction in the blood-vessels than in the normal. This change takes place also after removal of the superior cervical sympathetic ganglion.

The plethysmogram of the limbs (Oliver and Schaefer) may show a passive dilation, following the rise of the blood-pressure curve. However, when artificial means are taken to keep the general blood-pressure constant it is shown that the constrictions take place in the arterioles of the limbs also. This active constriction may be mechanically overcome, in ordinary experiments, as in Oliver and Schaefer's tests, by the enormous general rise of blood-pressure.

Studies on isolated organs show that perfusions of adrenaline solution produce vascular constriction. This, of course, indicates that the adrenaline effect is on the peripheral structures, but whether the

¹ Meltzer, S. J., and Meltzer, Clara: *American Journal of Physiology*, Vol. IX., p. 147, 1903.

stimulation is due to a reaction on the vasomotor terminal fibers or a direct stimulation of the smooth muscle has been far more difficult to determine. The classic work of Elliott,¹ and the later work of Dale,² have finally determined that adrenaline reacts at the myo-neural junction leading to stimulative or inhibitive end reactions according to the particular autonomic nerve mechanism considered.

Sollmann noted that isolated organs perfused with adrenaline

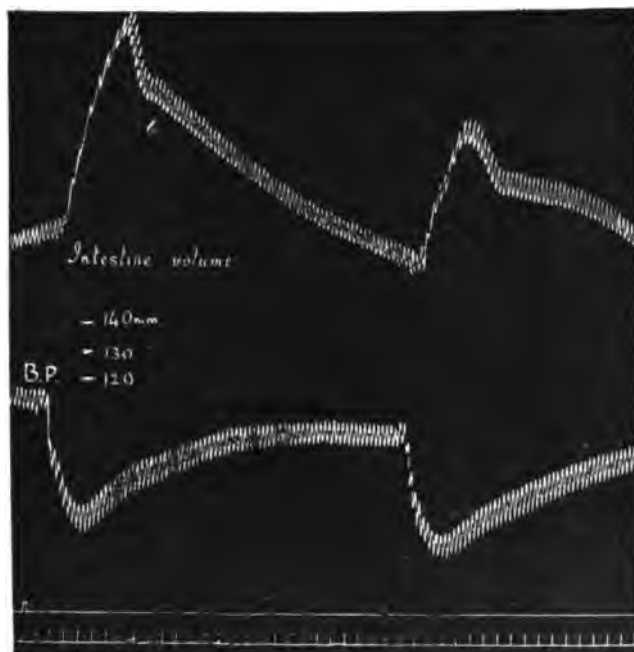


FIG. 39.—Shows the fall in blood-pressure and the increase in the volume of the intestine upon injection of successive doses of 0.1 mgr. adrenaline. The vasoconstrictor nerve-endings have previously been paralyzed by 100 mgrs. chrysotoxin. Dale.

solutions exhibited a constrictor effect followed by a late dilation. It is well known that certain visceral organs are doubly innervated, i.e., by antagonistic acting nerves. The above phenomenon is explained on the ground that the adrenaline, not only stimulates the nerve endings of the constrictor mechanism, but at the same time the ends of the dilator fibers. Since vasoconstriction is the dominant nerve influence, the dilator effects come on only after the former

¹ Elliott, T. R.: *Journal of Physiology*, Vol. XXXII., p. 401, 1905.

² Dale, H. H.: *Journal of Physiology*, Vol. XXXIV., p. 163, 1906.

have passed away. This phenomenon is rendered more intelligible when considered in connection with the well-known fact demonstrated by Bowditch and Warren that the vasodilator nerve mechanism retains its physiological properties longer after isolation from the central nervous system.

Dixon¹ showed that adrenaline was inactive after the sympathetic endings were poisoned with apocodeine. Dale has given us the cleaner cut analysis by demonstrating that ergotoxine in larger doses

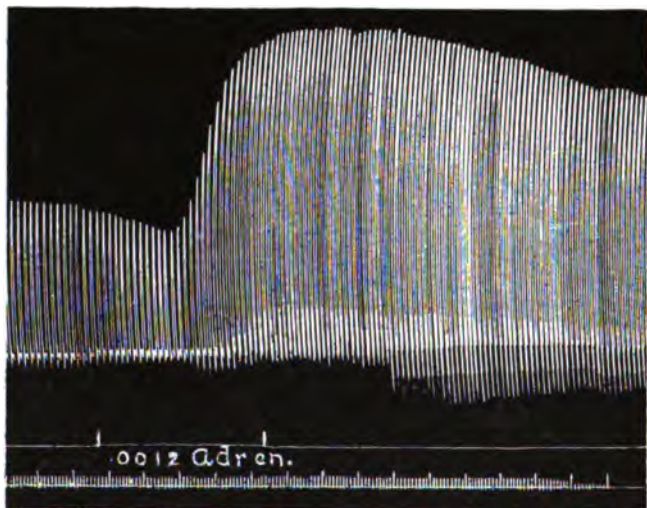


FIG. 40.—Epinephrine 0.0012 per cent. in Ringer's solution perfused through the frog's heart. Normal rate, 30; maximum rate, 35. The amplitude was increased more than 100 per cent. New tracing by Summers.

produces a selective paralysis of the sympathetic stimulative mechanisms without at the same time suppressing the function of the inhibitory mechanism. In his hands, adrenaline injected into the circulatory system, after the poisoning of the vasomotor nerve endings by ergotoxine, produced a sharp stimulation of the vasodilator nerves. In fact, this was true of the inhibitory nerves of all organs, i.e., not only of blood-vessels but of the inhibitory nerves of the visceromotor mechanism and of the uro-genital system, see table, page 159. In this clean-cut technique we have a means for the physiological separation of stimulative and inhibitory mechanisms, not only of the vascular system, but of other portions of the body as well. By the application of ergotoxine, it has been possible to demonstrate the fact that

¹ Dixon, W. E.: *Journal of Physiology*, Vol. XXX., p. 97, 1903.

adrenaline stimulates both inhibitory and motor mechanisms, when they arise by sympathetic nerve channels.

3. On the heart.—In the study of the action of epinephrine on the isolated heart, it is abundantly shown that it produces an increase in the rhythm and also in the amplitude of the contractions. This effect is true for both the frog heart and for the mammalian heart.

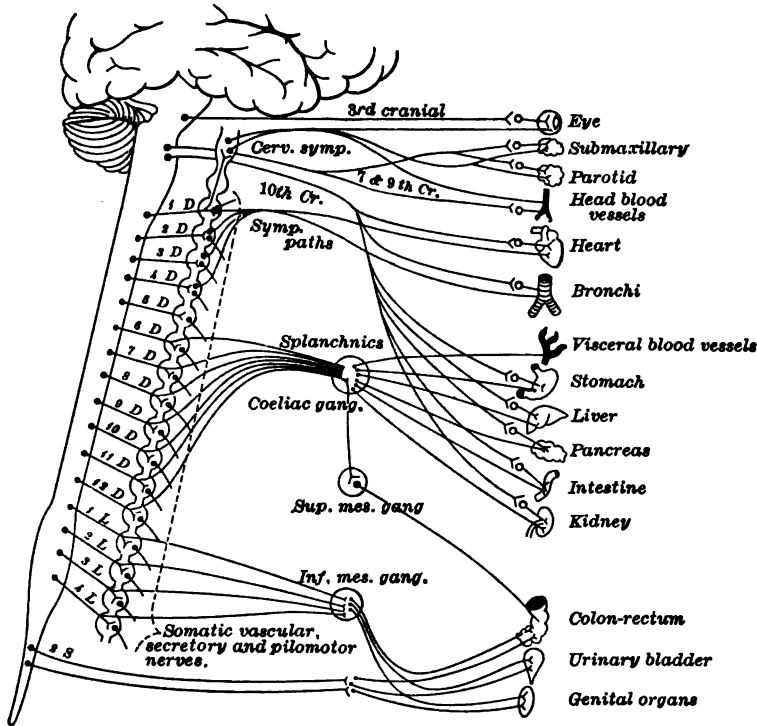


FIG. 41.—Diagrammatic representation of the paths of the autonomic nervous distribution. Modified from Meyer and Gottlieb.

A perfusion through the frog heart isolated from the central nervous system shows this acceleration accompanied by an increase in amplitude. In the perfused isolated mammalian heart the amplitude of the contractions will often be doubled or even trebled. The rate may follow the increase in amplitude or may remain constant. There is great variation in individual experiments.

If the heart is studied in the intact mammal, then the picture is somewhat different. At the stage of maximal blood-pressure, instead of an increase in heart rate there is a decrease, a fact attributed to the increase in tonic activity of the vagus center. The rise of

blood-pressure is itself sufficient to stimulate the vagus center—a fact that has long since been known. Hence many authors consider this vagus slowing under adrenaline as purely a secondary effect. The matter cannot be said to be fully settled, for it seems that there is a questionable factor of direct medullary stimulation involved. In any case, the stimulating effect on the accelerator mechanism is far more powerful and the quickest to take effect as shown by the accelerated heart rate during the rapid rise of blood-pressure. It is the predominant factor in determining the major change in heart function under adrenaline in the intact animal.

Cardiac muscle is itself directly stimulated by adrenaline. This is proved by experiments on isolated heart muscle. Strips of the terrapin's ventricle increase in amplitude and also in rate, under the influence of solutions of adrenaline. The accelerator cardiac mechanism is absent or at most poorly developed in this animal, hence the favorable muscular effects cannot be explained by assuming a stimulation of the accelerator endings.

4. Salivary glands.—The injection of adrenaline in mammals leads to an increased secretion of the salivary glands and of the lachrymal glands. The glands of the respiratory tract, in general, show acceleration in function, though there is apparently no stimulation of the sweat glands. Adrenaline stimulates the sympathetic secretion. This action of the drug is relatively unimportant.

5. On gastric and intestinal movements.—Brodie and Dixon¹ present a table showing that adrenaline influences all those organs that respond to sympathetic stimulation. The important function in the sympathetic control of the gastric and intestinal movements is through inhibitory nerves. These are primarily stimulated by adrenaline. Dale,² in the comparative table presented below, finds that adrenaline produces the same inhibitive action on the alimentary tract after ergotoxine as before poisoning by the drug.

The ileo-cecal sphincter (Elliott) is strongly contracted by adrenaline, though adjacent muscles on either side are inhibited by the drug, a result in complete accord with sympathetic stimulation.

6. Adrenaline on the uro-genital apparatus.—Adrenaline produces on the bladder and the uterus of the mammal the same general effects as are produced by stimulation of the sympathetic nerves. This Dale has shown to be both stimulative and inhibitive for the uterus, owing to the twofold sympathetic innervation.

¹ Brodie and Dixon: *Journal of Physiology*, Vol. XXX., p. 476, 1904.

² Dale, H. H.: *Journal of Physiology*, Vol. XXXIV., p. 163, 1906.

The Action of Adrenaline on Different Organs of the Mammalian Body in the Normal Animal, and after Ergot Poisoning. From Dale.

ORGAN.	Effects of stimulating the sympathetic nerve supply, or injecting adrenaline intravenously.	
	Before ergot.	After ergot.
Arteries (cat, dog, ferret).....	M	I
" (rabbit).....	M	Nil or weak M
Cardiac muscle.....	M	Nil or weak M
Spleen (cat).....	M	I
Stomach (cat).....	I	I
Small intestine (cat, dog, monkey).....	I	I
Large intestine (cat).....	I	I
Ileo-colic sphincter (cat).....	M	Nil
Internal anal sphincter (cat).....	M	I
Gall bladder.....	I	I
Fundus of urinary bladder (cat).....	I	I
Fundus of urinary bladder (ferret).....	M	I
Base of bladder and urethra (cat).....	M	Nil
Pilo-motor muscles.....	M	Nil
Dilator iridis.....	M	{ Nil with adrenal- ine. Weak M with cervical sympa- thetic stimulation
Uterus (cat, non-pregnant).....	I or M and I	
Uterus (cat, pregnant).....	M	
Uterus (rabbit).....	M	
Uterus (monkey).....	M	
Retractor penis (dog).....	M	Nil

M.—Motor effects.

I.—Inhibitory effects.

If the uterine motor nerves, which are dominant under certain conditions, are first paralyzed by ergotoxine, then injections of adrenaline stimulate the inhibitory nerves just as in the doubly innervated vascular regions. The uterus and vagina react together.

7. **On the eye.**—The intravenous injection of adrenaline produces a marked dilation of the pupil of the eye together with the usual vascular constrictions. On the other hand, local instillation of adrenaline in the normal eye produces no pupillary effect (Radzweisky, 1898), a failure that has been difficult to explain. Meltzer and Auer, 1904, in studying rabbits found that if the cervical sympathetic nerves were cut then adrenaline produced vasoconstrictions in the ear, both when given intravenously and when introduced hypodermically. The contractions of the vessels, under these conditions, came on later, were stronger, and lasted very much longer. The eye still responded as in the normal animal. After excision of the superior cervical ganglion the pupil of the eye was markedly dilated, not only by intravenous, but also by hypodermic and by local injections of

adrenaline. This dilation did not occur immediately after excision of the ganglion, but only after an interval of 24 hours or more, and it occurred as late as three and one-half months.

Undoubtedly the cervical sympathetic exerts a tonic mydriatic effect on the iris. Section of the nerve in the neck leads to a loss of

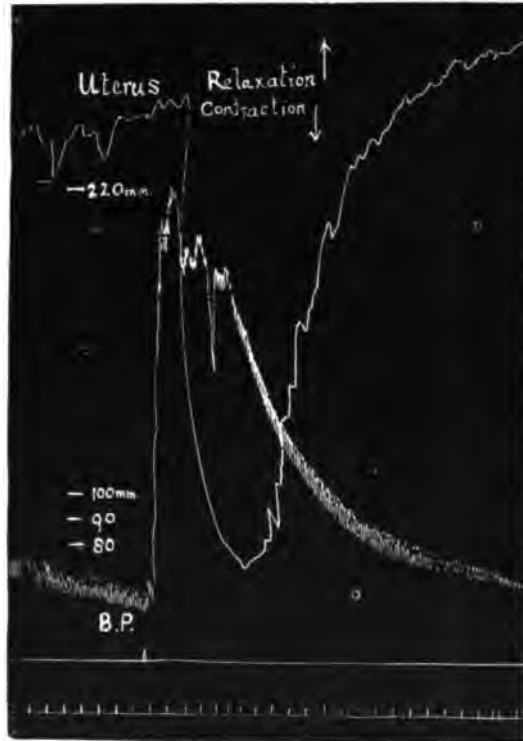


FIG. 42.—The action of 0.1 mgr. adrenaline injected into the circulation of the cat. B. P. arterial blood-pressure, lower tracing. The upper tracing represents the contraction of the pregnant uterus. Note from the table, page 159 that adrenaline causes relaxation of the non-pregnant uterus. Time in seconds. From Dale.

tone, hence to slight constriction of the pupil. Following excision of the ganglion the peripheral nerves will in time degenerate. Hence the mydriasis produced by injections or instillations of adrenaline at long intervals after the ganglion has been removed would seem to be dependent upon the local stimulation of the radial muscles. In what way the presence of the ganglion prevents this "paradoxical" action in the normal animal is not clear. The oculo-motor nerve is not influenced by adrenaline.

8. **Glycosuria.**—When adrenaline is administered to a mammal in stimulative quantity sugar appears in the urine. This is attributed to an increase in the glycogenolysis of the liver. The studies of Paton show that the glycosuria does not have its origin in the kidney. By operations on the rat which is a favorable animal for this purpose, it has been shown that extirpation of the suprarenal glands leads to the elimination of the stored glycogen from the liver. Schwarz¹ found from 2.44 per cent. to 5.07 per cent. glycogen in the livers of normal rats. After complete epinephrectomy, the two adrenals being removed in successive operations, the liver was never found to contain more than a trace of glycogen—in seven epinephrectomized livers, two only showed traces of glycogen.

IV.

General Discussion of the Action of Epinephrine.

Epinephrine, like the members of the pilocarpine group, produces its action chiefly at the terminal fibers of a special group of nerves, in this case the strictly sympathetic nerves, such as the accelerators of the heart, the inhibitory nerves of the stomach and intestine, etc.

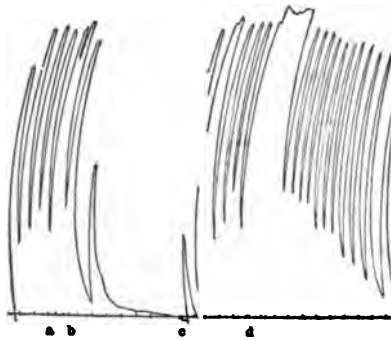


FIG. 43.—Intestinal strip beating in inactive blood which was removed at *a*. Blood from adrenal veins substituted at *b*, and removed at *c*. Contractions restored in inactive blood, blood removed at *d*; then blood from renal vein (same animal) added at *e*. Time in half minutes. From Cannon and de la Paz.

But of all the reactions the most specific and characteristic is the profound general stimulation of the vasomotor nerves. Here again we have a marked specificity of action and one which has a profound influence on the normal function of the body.

¹ Schwarz, Oswald: *Pflüger's Archiv*, Vol. CXXXIV., p. 259, 1910.

Cannon and de la Paz,¹ 1911, advanced the interesting view that the suprarenal gland is of specific physiological importance in connection with the function of the sympathetic system, particularly in times of stress. They observed that cats, dogs, and other animals when in fright show dilation of the pupils, erection of the hairs, inhibition of alimentary movements, etc.—typical sympathetic reactions. Under these conditions they say there is a strong stimulation of the suprarenal glands, whereby the secretion of epinephrine into the bloodstream is increased. This increase in turn reacts on the terminal structures of the sympathetic system in general to render physiological responses of the organs more effective.

That the suprarenals markedly influence metabolism is indicated by the disturbances of the glycogenic function upon their removal, or upon the injection of epinephrine. The same significance attaches to the disturbances of function that occur in disease of the glands, as, for example, in Addison's disease. Normal suprarenal glands contain from 2.5 to 3 per cent. adrenaline, whereas diseased glands may have little or none of this active principle.

The transient effect of epinephrine has been difficult to explain. As a matter of fact, the direct effect of epinephrine on cardiac muscular tissue is more persistent. The observations of Meltzer and Auer, already referred to, on the blood vascular constrictions and the mydriasis after excision of the superior cervical ganglion show that after this operation the action of adrenaline is very persistent, lasting one hour and often more. It would seem, therefore, that the transient effect is dependent in some way not fully explained upon the reactions through the sympathetic system. Of course, in paralysis or other loss of function of the nervous system the more enduring effect may be expected, and is to be kept sharply in mind by the clinician.

The disappearance of the vasoconstriction was at first thought to be due to oxidation of the adrenaline, either directly by the tissues or through the influence of the alkalinity of the blood and tissues. But it has been shown that the blood of an animal that has received a large dose of epinephrine and has apparently recovered from the effects still is capable of producing the adrenaline reaction in a second animal. Adrenaline injected into the leg of a rabbit, in which the circulation is obstructed by a ligature, will produce the typical reactions in the body when the ligature is removed. Contact with

¹ Cannon, W. B., and de la Paz: *American Journal of Physiology*, Vol. XXVIII, p. 64, 1911.

the tissues for one hour or more ought to suffice to oxidize the epinephrine if that accounted for its short reaction in the body.

The evanescent effect of epinephrine has been **against** its use as an ideal blood vascular stimulating agent for therapeutic purposes. But many conditions arise, disturbing the efficiency of the sympathetic nervous mechanism, such as a general vasomotor depression with atony of the blood-vessels. Here intravenous perfusions of warm saline containing not more than one drop of standard solution of adrenaline hydrochloride per 100 cubic centimeters, has proven extremely beneficial in overcoming the splanchnic vascular dilation in vasomotor shock. The peripheral action of epinephrine is beneficial even when the splanchnic dilation takes place from central shock. This would seem to indicate that epinephrine is a valuable agent in the transfusion of saline in this type of depressed sympathetic nerve function.

V.

Summary of Action.

Epinephrine intravenously injected produces a tremendous rise of blood-pressure. When given hypodermically the effect is slight unless the dose be very large—one hundred times as great as the intravenous dose. But it is effective and prolonged, especially in operative or degenerative removal of the peripheral sympathetic ganglia. The rise of blood-pressure is produced by strong stimulation of the arterioles primarily through the endings of the vasomotor nerves, or in cases of paralysis of the post-ganglionic nervous mechanism through direct stimulation of the muscular tissue.

Arterial constriction occurs through the body, but is greatest in the splanchnic area. The heart itself is stimulated through the accelerator nerves and by an increase in contractile power of the heart muscle. This effect is somewhat counteracted by the increase in tone of the cardiac inhibitory center, which effect is at its maximum at the time of maximal blood-pressure. Other organs respond to epinephrine by an increase of function of the type produced by the stimulation of the sympathetic nervous mechanism. The organs of chief importance are the eye, in which dilation of the pupil occurs on intravenous injection of epinephrine, or in local application or subcutaneous injection after removal of the superior cervical ganglion; the stomach and intestine, in which there is an inhibition of peristalsis accomplished through stimulation of the sympathetic inhibitory nerves; and on the bladder, uterus, and spleen, where similar effects

are produced. Metabolism is sharply influenced by adrenaline, shown primarily by the increase in the glycogenolysis of the liver.

This active principle is produced by the suprarenal gland under the nervous control of the sympathetic nervous system. The alkaloid is discharged into the blood-stream and distributed especially to the nerve endings of the sympathetic fibers throughout the body which it specifically stimulates, and to the muscular and glandular tissues controlled by these fibers. Epinephrine is largely consumed in the body, though when excessive quantities are present, small amounts are excreted through the urine.

CHAPTER XVII.

THE ERGOT SERIES.

I.

Historical and Chemical.

The fungus, *Claviceps purpurea*, which grows chiefly on rye, contains a series of pharmacologically active principles more or less toxic. Preparations of ergot have been used in medicine since the sixteenth century. The active principles have been difficult to isolate but have been the subject of numerous careful studies. The first important investigation which should be mentioned is that of Kobert¹ in 1884. Kobert isolated three substances, to which he gave the names ergotinic acid, sphacelinic acid, and cornutine. Kobert's active principles have been proven to be in all probability impurities. However, he showed that ergot contained two types of toxic substances, one of which leads to chronic disintegration and sloughing of the tissues, the other to more acute conditions associated with high blood-pressure and accompanying nerve symptoms.

In chronic ergotism, resulting during severe epidemics which have occurred in certain parts of Europe following the use of infected rye bread, these two types of intoxication have occurred.

Through the mutually supporting chemical and pharmacological work of Barger and Dale,² in combination with various associates, we now know that the activity of ergot is due primarily to three chemical substances. These chemicals are ergotoxine, isoamylamine, and the more strongly toxic parahydroxyphenylethylamine. The latter approaches adrenaline in the character of its action.

Ergotoxine, $C_{22}H_{21}O_5N$.

Isoamylamine, $\begin{matrix} CH_3 \\ CH_2 \end{matrix} \rangle CH.CH_2.CH_2.NH_2$

¹ Kobert, R.: *Arch. f. Path. u. Pharm.*, Vol. XVIII., pp. 316-380, 1884.

² Barger, G., and Dale, H. H.: *Bio-chemical Journal*, Vol. II., pp. 240-299, 1907; *Journal of Physiology*, Vol. XLI., p. 19, 1910.

Parahydroxyphenylethylamine, $\text{HO} \langle \text{C}_6\text{H}_4 \rangle \text{CH}_2.\text{CH}_2.\text{NH}_2$

Adrenaline, $\text{HO} \langle \text{C}_6\text{H}_3(\text{OH}) \rangle \text{CH}(\text{OH}).\text{CH}_2.\text{NH}.\text{CH}_2.$

Isoamylamine and parahydroxyphenylethylamine, the latter known under the trade name of tyramine, were isolated from ergot by the methods used in isolating the same substances from putrid meats,¹ and it is interesting to note that the probable origin is similar in the two cases, namely, from leucine in the first instance and from tyrosine in the second. The pharmacological reactions are identical in kind.

The complex content of ergot preparations readily decomposes, hence such preparations rapidly change in the intensity of their physiological actions, a factor that should be taken into account in the therapeutic application of the drug.

II.

Outline of Pharmacological Action.

The pharmacological action of individual ergot preparations varies, but when preparations of the crude drug are used the following primary effects occur:

1. *Stimulant effects on plain muscle organs, prominent among which are the circulatory system, the alimentary canal, and the urogenital system.*
2. *Specific toxicity to the motor types of myo-neural junction (ergotoxine).*
3. *Toxicity to protoplasmic structures in general.*
4. *Parahydroxyphenylethylamine produces a sympathomimetic activity comparable to epinephrine.*
5. *Ergotine produces primary stimulation followed by paralysis of the myo-neural junction.*

III.

Details of Pharmacological Action.

1. **The action of chemically pure principles.**—The exact action of the ultimate principles in ergot is still under some discussion in the

¹ Barger, G., and Walpole, G. S.: *Journal of Physiology*, Vol. XXXIX., p. 343, 1909.

literature, but accepting the work of Barger and Dale, as indicated above, we may attribute the characteristic ergot symptoms, first, to *ergotoxine*, which is responsible for the gangrenous degenerations attributed to ergot, and second, to the *parahydroxyphenylethylamine*, the blood-pressor and other involuntary motor effects.

2. *Ergotoxine*.—Ergotine produces "ataxia, dyspnea, salivation, gastro-intestinal irritation, and gangrene." It also produces stimulation of those organs containing smooth muscle, especially the

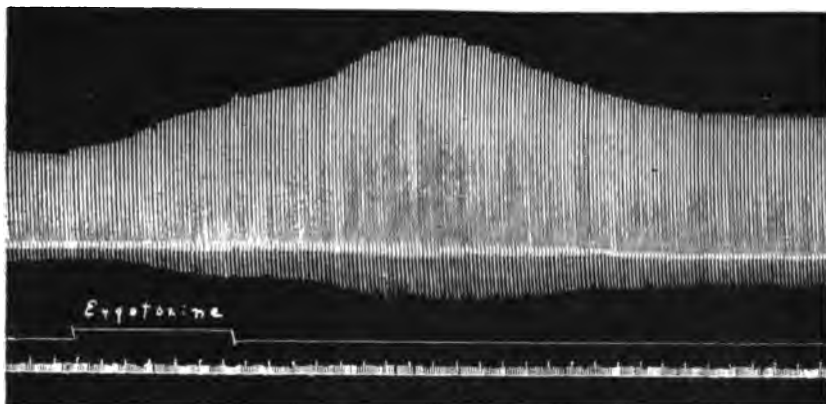


FIG. 44.—The action of ergotoxine perfused through the frog's heart. The rate is little changed though the amplitude is slightly increased and remains high after the normal Ringer's solution is returned. New tracing by Summers.

uterus and the arteries. In these latter paralysis follows at a later stage of its action. It is an interesting fact that the extreme toxicity of ergotoxine is lost by its dehydration, in the crystalline ergotinine $C_{35}H_{39}O_5N_5$. It is the ready transformation between these two substances to which is ascribed much of the variability in current preparations of ergot. Barger and Dale believe that the active ergotoxine has been present as an impurity and accounts for the action ascribed to many of the specific substances that were prepared earlier in the history of the study of ergot.

3. *Isoamylamine*.—This active principle has been tested out by Dale and Dixon, who found that it was a positive blood-pressure producing substance. Its reaction is not so vigorous as the other active ergot principles, and its quantity is relatively small in ergot, hence it may be passed without special emphasis.

4. *Parahydroxyphenylethylamine*.—This substance was isolated from ergot by Barger and Dale in 1909, and was carefully studied

pharmacologically by Dale and Dixon. They found it to be a very strong pressor principle. It caused a vigorous rise of blood-pressure when injected intravenously in as low as two-milligram doses. It also sharply stimulated the amplitude and rhythm of the heart, the contractions of the spleen, the uterus, and of muscular portions of the urinary apparatus. The action is indeed very similar to that of

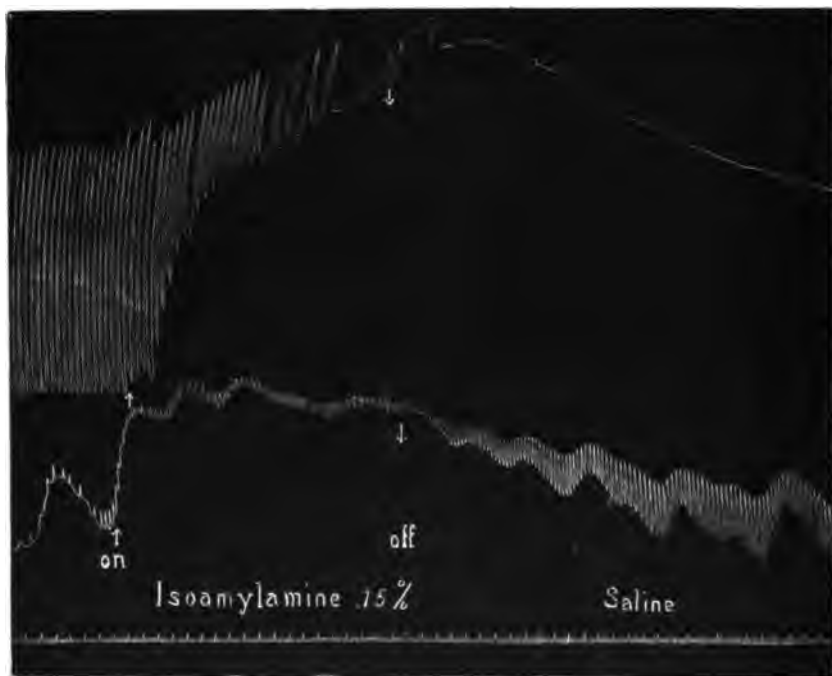


FIG. 45.—The influence of isoamylamine on strips of muscle from the terrapin heart. The upper tracing is a ventricular, the lower a sinus-auricular strip. The strength of solution 15 per cent. in physiological saline. The most striking change is the marked increase in tone and suppression of the rhythm in the ventricle. Both strips exhibit a strong rhythm in the late after-period. New tracing by Stone.

adrenaline, producing both the motor and inhibitory effects characteristic of nerves of the sympathetic system. The motor effects are more powerful than the inhibitory. However, the stimulating action of the drug is many times less intense than that of adrenaline.

5. The action of extracts of ergot.—The pure principles of ergot have not yet been fully accepted for general use. Theraputists still find the principal available preparations to be the older Galenic extracts, or the more or less purified extracts. The extracts of ergot contain beside the pure principles mentioned above traces of a num-

ber of more or less toxic substances, some of which have deleterious effects, particularly on the heart. As these principles vary in quantity in different preparations the extracts should, like digitalis, always be physiologically standardized and should be used within a reasonable time after this standardization.

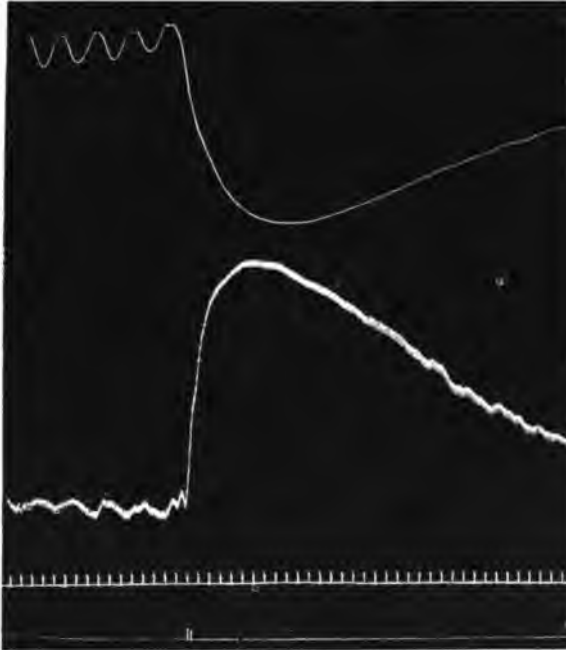


FIG. 46.—The effect of 2 mgrs. p-hydroxyphenylethylamine given intravenously. Spleen volume upper, and blood-pressure lower curve. Time in 10 seconds. Pithed cat. From Dale and Dixon.

The most typical and characteristic influence of ergot is the production of an increased action of smooth muscle tissue. The therapeutic value of the drug depends especially on this reaction as regards, first, the function of the uterus, and second, the reactions of the blood vascular system.

6. **The action of ergot on the uterus.**—For many years ergot has been used for its beneficial effect upon the contractions of the uterus during parturition. When given in therapeutic quantity it leads to an increase in the expulsive uterine contractions during childbirth, especially when the uterine wall is reacting weakly. In excessive or toxic doses the normal peristaltic contractions may become

tetanic in character, which, of course, is detrimental to the normal function at this time. Over-violent contractions against the volume of the fetus may in fact lead to laceration and rupture of the uterus, as well as asphyxiation of the fetus itself.

A second obstetric use of ergot is to aid in the post-partum contractions of the uterine wall in order that the open and bleeding

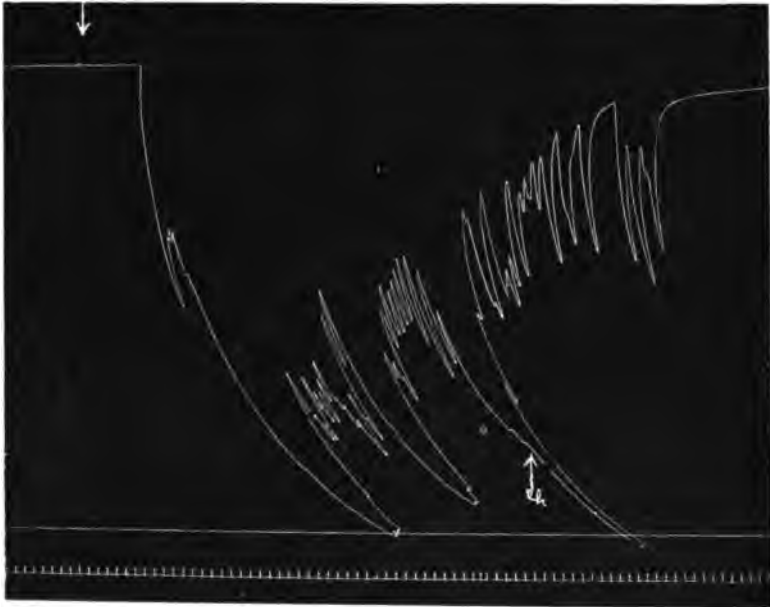


FIG. 47.—The effect of 2 mgrs. of parahydroxyphenylethylamine on the isolated apex of the pregnant uterus of the cat. The drug was added at the ↓ and changed to pure Ringer's solution at the ↓. Contractions, down strokes. Time in 10 seconds. From Dale and Dixon.

uterine sinuses may be somewhat closed during the critical time that these lacerated surfaces are being occluded through blood coagulation, etc. There is no doubt that a favorable exhibition of the drug is of value in this connection, though its excessive use may lead to an after-paralysis and relaxation with post-partum bleeding.

In following the reactions of the uterus to ergot it must be kept in mind that the organ has a double innervation, stimulative motor nerves, chiefly through the hypogastric and the inhibitive nerves, in part from the sacral region. The relative physiological control of these nerves over the organ varies according to the state of the uterus. Numerous experiments have shown that the pregnant uterus is much

more amenable to the motor nervous control than the non-pregnant. Ergot, for example, often causes relaxation of the virgin uterus, whereas it produces strong contraction of the pregnant uterus. The ergotoxine first stimulates, then paralyzes the utero-motor apparatus, apparently paralyzing at the myo-neural junction. After this paralysis epinephrine, which stimulates both motor and inhibitory uterine nerves, now produces only inhibition.¹ The ergotoxine constituent of extracts of ergot may through this latter effect modify the pressor influence of the parahydroxyphenylethylamine.

7. **The action of ergot on the circulatory system.**—Sollmann and Brown² have exhaustively studied the influence of ergot on the circulatory system, showing the remarkable variation in the intravenous effects of these preparations. They more often found a fall of blood-pressure on intravenous injection of ergot than the contrary. This, in view of the well-established blood pressor action of both ergotoxine and of parahydroxyphenylethylamine, shows the inherent danger of reliance on extracts of ergot. The logic of the case would indicate the greater reliability of the chemically pure preparations. The therapeutically valuable principles of ergot produce a tremendous rise of blood-pressure by a stimulation of the vasoconstrictor nerve endings. The vascular contraction is similar in character, but smaller in amount and more prolonged than that produced by epinephrine.

The gangrene that follows the use of certain ergot preparations has been explained on the ground that the vascular spasm of such vascular peripheral organs as the ear and the cockscomb is due to the fact that the prolonged contraction shuts off the blood-supply to such an extent as to cause asphyxiation and degeneration of the tissues. Histological studies have shown obliteration of the cavity of the blood-vessels accompanied by hyaline degeneration. However, this explanation may account only in part for the gangrene effects, since many preparations of ergot contain considerable quantities of saponine-like bodies.

8. **On the heart.**—The cardiac action is decidedly strengthened by ergot, especially is the amplitude of the contraction of the ventricles increased. This is shown not only on the heart in place, but on the isolated heart (Sollmann and Brown), and is therefore to be ascribed to peripheral action, and is due to stimulating effects on the accelerator nerve endings. In contrast with the cardiac stimulation of alkaloids

¹ Dale, H. H.: *Journal of Physiology*, Vol. XXXIV., p. 163, 1906.

² Sollmann, Torald, and Brown, E. D.: *Journal of the American Medical Association*, Vol. XLV., p. 229, 1905.

such as epinephrine, it is noted that the ergot stimulation is much more persistent and prolonged. Epinephrine stimulates the accelerator nerve endings in cardiac muscle, and the resulting physiological changes are quickly developed and profound in volume though rel-

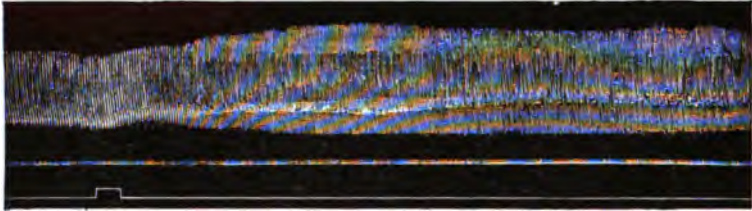


FIG. 48.—The effect of 0.2 mgr. of parahydroxyphenylethylamine on the isolated heart of the rabbit. Time in 1-4 seconds. From Dale and Dixon.

atively short in duration. The cardiac action of the active principles of ergot is somewhat more prolonged, though otherwise similar to epinephrine, a fact which undoubtedly is to be ascribed as chiefly due to the parahydroxyphenylethylamine constituent. However, the

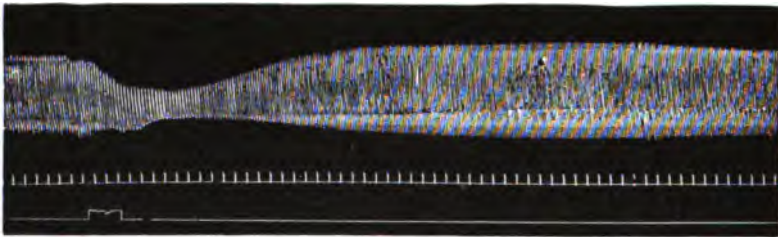


FIG. 49.—The effect of 0.2 cc. $\frac{N}{10}$ solution of isoamylamine hydrochloride on the isolated heart of the rabbit. Time in 2 seconds. From Dale and Dixon.

isoamylamine constituent also stimulates after a very brief muscular depression, as shown in the figure. Augmentative influence on the heart produces a strong percentage of the rise in blood-pressure. It is the combination of the two factors, increase in peripheral resistance and cardiac augmentation, that accounts for the firm, hard pulse in ergot poisoning. In those preparations of ergot which have cardiac depressing principles the stimulating effect may be counteracted by the direct cardiac muscular depression.

9. Action on the alimentary canal.—Ergot leads to a marked increase of the peristalsis of the alimentary tract. Not only does this systemic effect result, but local irritations may lead to pro-

nounced insalivation, vomiting, and purging. The peristaltic action is ascribed largely to the effect of ergot on the nervous mechanism controlling alimentary peristalsis, though a direct stimulation of the smooth muscle has been described. Gangrenous foci are also found in the mucous membrane and walls of the alimentary canal. These are due to the vascular stagnation and resulting local degenerations from the action of ergotoxine.

10. Effect of ergot on other physiological mechanisms.—The nerve centers in the medulla are stimulated to some slight extent by ergot, though it has not always been clear whether or not these stimulations are the indirect effects of the change in vascular supply.

The secreting glands are influenced to a greater output, the eye exhibits a marked contraction of the pupil, and the urinary bladder is thrown into motor activity, all by intravenous injections of ergot. These effects are doubtless due primarily to the two most active constituents, ergotoxine and hydroxyphenylethylamine.

D. *Drugs With Primary Activity On Smooth Muscle.*

CHAPTER XVIII.

BARIUM CHLORIDE.

I.

Barium chloride, one of the inorganic salts, has a very pronounced influence on the circulatory system, an action in a way intermediate between that of digitalis and ergot.

II.

Outline of Pharmacological Action.

Barium chloride is a very toxic substance and produces toxic change in the physiological reactions in most parts of the body, summarized as follows:

1. *A pronounced stimulation, followed by a toxic paralysis of the central nervous axis, especially of the medulla and cord.*
2. *Vascular constriction by direct stimulation of the muscles of the arterioles.*
3. *Increase in the heart rate, with fibrillation in the toxic stage.*
4. *Respiratory acceleration from medullary stimulation.*
5. *A toxic contraction of skeletal muscles, with delay in the relaxation phase.*
6. *Cathartic and diuretic action.*
7. *Local irritation and toxic necrosis of tissue.*

III.

Details of Pharmacological Action.

1. **Barium chloride on the circulatory system.**—On the heart: The most striking influence of barium chloride is that on the circulatory system. The function of the heart is decidedly influenced. In therapeutic quantity introduced into the general circulation, the heart beats stronger but slower, but a greater quantity (30 mgr.

intravenous in a dog) leads to a tremendous increase in the heart rate.

On the isolated perfused heart the contractions are more vigorous and far more rapid than under normal conditions. The peripheral action of barium chloride is directly on cardiac muscle. Isolated strips of ventricle contract with greater amplitude and with increased rhythm. There is a tendency to great increase in tone, so that the muscle enters a strong systolic contracture. If the concentration of the salt be too great or it act too long, the contrac-

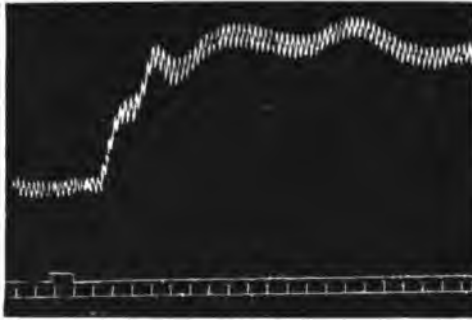


FIG. 50.—The effect of 5 mgrs. of barium chloride on the blood-pressure after paralysis of the vasomotor nerve endings by 150 mgrs. of chrysotoxin. This demonstrates that the barium chloride acts directly on the smooth muscular tissues of the arterioles. From Dale.

tions cease to be coördinated. Independent rhythmic centers are set up over the heart, leading to fibrillation. This effect of barium chloride is produced by 0.01 per cent. (1 in 10,000) in physiological saline. Perfusions of barium chloride solutions through the isolated mammalian heart produce changes that are quite comparable to the muscular actions just described. The rhythm is increased, the volume of the contractions is greater, and there is a marked tendency toward fibrillation.

When the heart is studied in its normal relations it shows a decided slowing, due to the preponderant influence of barium chloride on the cardiac inhibitory center. But if the vagus nerves are first cut, then there is a primary acceleration of rhythm.

2. **On the peripheral arterioles.**—Barium chloride solutions increase the peripheral resistance of the circulatory bed by contractions of the arterioles. The reaction is due in part to stimulation of the vasomotor center, but in larger part to peripheral muscular action, as shown by the great decrease in volume observed in the plethysmo-

graphic measurements of isolated organs. The contractions occur also after drugs which poison the nerve endings and are therefore to be ascribed to a direct stimulation of the smooth muscle in the walls of the arterioles.

3. **Barium chloride on the alimentary and uro-genital muscle.**—The alimentary canal is actively stimulated to increased peristalsis. In both the gastric and the intestinal regions the changes are very pronounced. This influence is in large measure a direct action of the barium chloride on the smooth muscle walls. For the same reason the walls of the uterus and urinary bladder have their typical muscular movements decidedly increased.

4. **On skeletal muscle.**—Skeletal muscle is rendered more unstable and irritable by barium chloride. When a test is made by a series of contractions of an isolated muscle it is found that the amplitude of the contractions is sharply increased in the earlier numbers of the series, while contracture from delayed relaxation makes its appearance later in the series, but long before the muscle is exhausted.

5. **On the central nervous system.**—Barium chloride is a toxic substance for the nervous tissue. Its influence is characterized by prolonged and violent stimulation with paralysis in the later stages. Practically all the basic nerve centers have their irritability sharply increased. The spinal cord, for example, is far more sensitive to reflex stimulation and shows a tendency to the discharge of reflex spasms that approach the character of tetani.

Most typical nerve changes are shown by the disturbance of function of the reflex centers of the medulla. The vasomotor center is increased in tone and stimulated, the cardiac inhibitory center stimulated, and the influence on the respiratory center leads to a great acceleration of respiratory rhythm and amplitude. Intravenous injections of non-toxic quantities of barium chloride produce on the respiratory center at first a great acceleration in rhythm, which may amount to as much as 100 to 150 per cent. of the preceding normal. This enormous increase of rhythm is associated with a great increase in respiratory amplitude. This stage is followed by a marked diminution in amplitude, usually with the prolonged maintenance of the supra-normal rate. Recovery is slow and characterized by irregularity of respiratory rhythm.

6. **The local action of barium salts.**—Barium salts are extremely toxic. When brought into contact with mucous membranes or injected hypodermically they tend to produce disintegration and necrosis

of the local area. This is due to a toxic action on protoplasm in general.

7. Therapeutic indications.—Pharmacologically the reactions of barium in the body strongly suggest a comparison with the digitalis series. Various attempts have been made to introduce it into therapeutics with indifferent success, chiefly from its dangerous toxic after-effects. It has been cautiously exhibited in conditions of extreme atony, especially of the circulatory system. Barium chloride was recognized in 1910 and 1911 only by insertion into *New and Non-official Remedies*, with the following description under the caption, "Actions and uses": "Barium chloride is a toxic substance, its most striking effects being exerted upon muscle tissue, especially unstriated and heart muscle. In large doses it affects the spinal cord and medulla. By actively stimulating peristalsis, through action on the muscle wall, and by its direct irritant action, it readily produces vomiting and purging. It strengthens the cardiac contraction by direct action of the heart muscle, and by this means and still more by direct action on the vessel walls it greatly increases blood-pressure, acting like digitalis. It acts on the muscles like veratrine. It first greatly excites and then paralyzes the spinal cord and medulla. Given in very dilute solution, absorption is small and the barium is deposited in the bones. Injected intravenously it causes tonic and clonic spasms, because of stimulation of the spinal cord and medulla.

"In fatal doses it causes hemorrhages into the stomach, intestines, and kidneys.

"Its clinical use has been attended with little success, chiefly because of the gastro-intestinal irritation and high toxicity. It has, however, been used in cardiac disease with insufficient blood-pressure, as a general tonic, and with less reason in tremors, in sclerosis of the central nervous system, internally and locally in varicose veins, etc. Its use is attended with considerable danger."

CHAPTER XIX.

THE NITRITES AND THE NITRO-GLYCERINES.

I.

Chemical.

As illustrations of a group of drugs acting particularly on the circulatory system, but to produce effects of depression of function just the opposite of ergot, barium chloride, etc., the nitrites form the most important example.

Sodium nitrite, NaNO_2 , is a soluble salt. Amyl nitrite is a highly volatile, amber-colored liquid, which can be taken as a representative of the derivatives of the methane series, in which the alkyl is attached by an atom of oxygen, as shown in the formula, $\text{CH}_3\text{O.NO}$, etc. The tri-nitrate of glycerine, or nitro-glycerine, $\text{C}_3\text{H}_5(\text{NO}_3)_3$. This substance is readily decomposed in the alkaline fluids of the body, giving off nitrites and nitrates, the latter being inactive in small quantities, while the former give rise to the usual nitrite functional reactions.

II.

Outline of Pharmacological Action.

1. *Marked depression of blood-pressure produced through (a) a decrease in the functional activity of the smooth muscle, and (b) depression of the cardiac nervous mechanism.*
2. *The formation of methemoglobin.*

III.

Details of Pharmacological Action.

1. **On the circulatory system.**—The most characteristic physiological change produced by the nitrites is that of relaxation of muscular tissue, and particularly in the circulatory and respiratory mechanisms. When sodium nitrite is given intravenously, or amyl nitrite given either intravenously or by inhalation, there is a marked and prolonged fall of blood-pressure. This circulatory effect is pri-

marily due to dilation of the arterioles. The skin is flushed and the great vascular beds in the abdominal viscera are congested.

The perfusion of isolated organs is accompanied by a similar evidence of peripheral dilation. There is a more rapid outflow of the perfusion fluid, and if the organ be inclosed in a plethysmo-



FIG. 51.—Showing the action of nitrites on the form of the human pulse. *A*, normal pulse; *B*, immediately after amyl nitrite vapor; *C* and *D*, successive later stages in the return to the normal.

graph, increase in volume occurs. If the organs be studied in their normal relations, as, for example, portions of the abdominal viscera, it can be shown that the nervous mechanisms are still functional, though less actively so. Stimulation of the splanchnic nerve produces a slight constriction of its terminal visceral bed. This constriction is less pronounced than in the normal, a fact, which, together with those related above, leads to the conclusion that the action of the nitrites is on the smooth muscle itself.

2. On the heart.—Dilation of the blood-vessels, associated with fall of blood-pressure produces a physiological condition, which acts as a stimulus to increase the heart rate. Increase of heart rate is also brought about by any condition which diminishes the tone of

the vagus center, or, on the other hand, increases the contractile power of the cardiac muscle, as by barium chloride.

When the nitrites are given the heart rate is sharply increased, but the amplitude of the contractions is practically unchanged. In studies of the isolated hearts of both the frog and the mammal, the increase of rate is less marked, but enough to indicate that the nitrites do slightly add to the irritability of cardiac muscle, though this effect is accomplished only by very minute doses. The stronger action of the nitrites is to depress cardiac muscle, much in the same way as it depresses smooth muscle.

3. **On the respiratory apparatus.**—Nitrites have proven to be active depressants of muscular contractions in the respiratory apparatus. The drug acts directly on the smooth muscle of the bronchioles, producing a relaxation of these muscles and dilation of the bronchioles. This effect is of value in clinical conditions, such as in asthma. Respiratory acceleration is generally noted, an effect which is due in mild extent to stimulation of the respiratory center. The depressed circulation through the respiratory center has a secondary effect, which must not be forgotten in this relation, an effect which is thought by some to be adequate to explain the acceleration noted.

4. **The formation of methemoglobin.**—The nitrites are methemoglobin formers. There is not the disintegration of the corpuscles to the extent noted in pyrogallol poisoning.

IV.

Condensed Summary of Action.

The nitrites and the nitrite liberators are of peculiar value in that they produce relaxation of structures depending for their action upon smooth muscle. For example, the blood-pressure falls from arteriole dilation, and the effect is accompanied by a direct depression of the function of the smooth muscles of the arteriole walls. The heart is accelerated, largely from depression of the inhibitory mechanism, but in part through an initial though slight increase of irritability of cardiac muscle. Respiratory spasms of the bronchioles are relieved by relaxation of their smooth muscle. There is some toxic formation of methemoglobin accompanied by the secondary symptoms, which result from a lack of sufficient oxygen carried by the blood.

Nitrites in therapeutic quantity are peculiarly valuable to relieve smooth muscle spasms wherever they occur throughout the body, as, for example, in asthma, angina pectoris, lead poisoning, etc.

E *Glucosides of the Digitalis Series.*

CHAPTER XX.

THE DIGITALIS GROUP.

I.

Historical and Chemical.

Under the digitalis group one may classify a series of plant and animal substances, which have a rather extreme toxicity to animal



FIG. 52.—*Digitalis purpurea*, Foxglove, the plant in full bloom, a flower about two-thirds size, and a section natural size. Baillon.

tissues in general, and are particularly stimulative and toxic to the heart and circulatory system.

The substances of this series are derived from a rather wide range of plants, of which the most important are members of the genera *Digitalis*, *Strophanthus*, and *Scilla*. Of a long series of genera yielding active principles, but of more or less secondary importance, may be especially mentioned *Apocynum*, *Helleborus*, *Convallaria*, *Antiaris*, and *Erythrophleum*.

For the most part these plants yield non-nitrogenous glucosides and resinous principles. The active substances of the digitalis species were first separated by Schmiedeberg¹ and have later been studied by several authors. The active principle of *Strophanthus*, strophanthin, has also been separated, and has a therapeutic value similar to that of digitalis. Of these substances the most important are:

Digitalin.
Digitalein.
Digitophylline.
Digitoxin.
Strophanthin.

Preparations of the glucosides readily decompose, giving rise to toxiresins, in which their physiological reactions are markedly changed in the general direction of increased toxicity.

II.

Outline of Pharmacological Action.

The different active principles have somewhat varying effects in the body, but in general they all produce:

1. *In therapeutic quantity an increase in the function, and in toxic quantity paralysis of practically all the tissues in the body.*
2. *Specific stimulation of the heart muscle.*
3. *Stimulation of the cardiac inhibitory nervous mechanism.*
4. *Specific stimulation of peripheral arterioles, particularly strong on the splanchnic region.*
5. *Stimulation of the vasomotor center of the medulla.*
6. *A marked diuretic action.*
7. *A tonic action on the central nervous system, and on endothelial and lymphatic tissues.*

¹ Schmiedeberg: *Arch. f. Exp. Path. u. Pharm.*, Bd. 3, S. 16, 1875.

8. *Local irritation and inflammation when applied hypodermically, or to mucous surfaces.*

III.

Details of Pharmacological Action.

In the study of the details of the change in physiological function induced by the different members of this series we will take as a standard for comparison the action of soluble digitalis and of strophanthin.

1. **Action on the circulatory system.**—Digitalis produces its primary, one might almost say specific, action on the circulatory system. The therapeutic effects are (1) stronger and slower heartbeat, (2) general vascular constriction, and (3) a pronounced increase in blood-pressure. The details of these changes must be given before general discussion of their inter-relations.

2. **The heart.**—Digitalis given to a living mammal by the mouth usually produces a stronger, slower, and more efficient beat of the heart. Keeping in mind the complicated nervous and muscular arrangements of this organ, we may summarize by saying that the direct cardiac effects of the digitalis series are:

1. Stimulation of the cardiac muscle, producing increased amplitude and usually an increase of the rhythm of contraction, and a greater irritability of the tissue.

2. Stimulation of the cardiac inhibitory nervous mechanism by strong direct action on the vagus center, together with weaker local action in the heart ganglia. This produces slowing and greater relaxation of the heart.

These two factors, i.e., the direct muscular effects and the vagus nerve effects, are diametrically opposed to each other, hence many of the characteristics of the heartbeat under digitalis in the body are to be interpreted through their algebraic addition.

Secondary effects on the heart are produced because of the tremendous rise of blood-pressure following the peripheral vasoconstriction. This rise of pressure in itself increases the irritability of the medullary centers, therefore the vagus tone, and produces a mechanical stimulation of the sensory end organs of the depressor nervous mechanism, which Eyster and Hooker have shown to be located in the walls of the aorta.

An experimental analysis of the heart effects of digitalis can be made by studying:

1. Isolated heart muscle.
2. The isolated heart.
3. The heart *in situ*.

Isolated pieces of cardiac muscle, of the terrapin or of the cat, have their irritability sharply increased by members of the digitalis series—digitalin, strophanthin, etc. True, it requires a rather

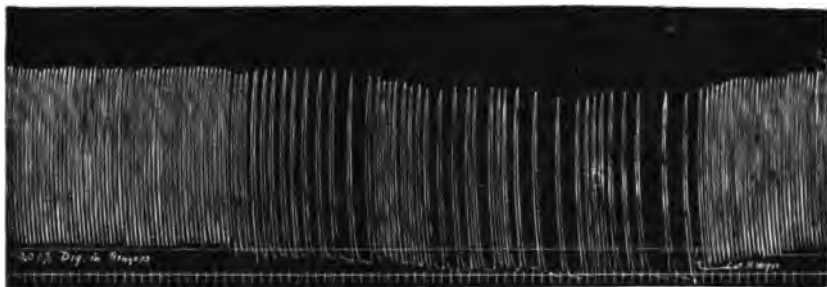


FIG. 53.—Action of digitalis on the cardio-inhibitory center. During the time marked 0.01 per cent. digitalin was perfused through the isolated brain of the terrapin, vagus nerves intact, general circulation isolated from the brain. At the point marked the right vagus was cut, the heart immediately escaped. Cutting the left vagus during this experiment induces no change in rate. Time in 5 seconds. New tracing by Peeler.

stronger dose, but both the amplitude and the rate of the heart muscle contractions are favorably influenced. With a relatively strong dose the terrapin ventricular muscle has its systolic phase increased and its relaxation hindered so that a state of tonic contracture supervenes.

3. *The isolated frog's heart.*—Perfusions of the isolated frog's heart show phenomena similar to those obtained from the muscle alone. The rhythm is slightly accelerated, but the greatest change consists in the increase in the systolic and decrease in the diastolic phase of the contraction. The net result is a tendency of the heart to remain in systole. In the tonic stage this condition becomes dominant.

The contractions of the auricles of the perfused frog's heart are much more complete, and the relaxations relatively more incomplete than is the case with the ventricle. However, in experiments a slight excess of mechanical pressure may obliterate this effect and the auricles will remain dilated.

4. *On the isolated mammalian heart.*—The isolated mammalian heart studied by the coronary perfusion method is most instructive. Here very dilute solutions of soluble digitalin, 11 parts to 1,000,000 of

perfusing solution, produce a sharp increase in the amplitude with only slight, if any, variation in the rate. If the dosage be increased, then both amplitude and rate are strongly increased. These effects are interpreted as primarily muscular. With perfusion of a toxic concentration the heart becomes irregular in its rhythm. Independent rhythmic centers are set up in the ventricular muscle, together with arrhythmia of the auricles and ventricles. This condition comes on rapidly and ends in fibrillation and death in the systolic stage.

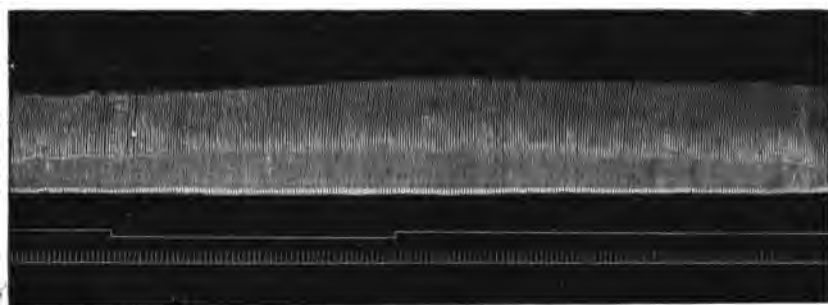


FIG. 54.—Digitalis on the isolated mammalian heart, dog. The heart was kept contracting rhythmically by coronary perfusion with oxygenated Ringer-blood, 1 to 3. During the time indicated by the signal marker 0.0005 per cent. of digitalis in Ringer-blood solution was perfused. The rhythm of the heart remained absolutely constant during the experiment. The increase in amplitude amounted to 14 per cent. just before perfusion of digitalis was stopped, but increased to 19 per cent. in a few seconds after the normal was re-established. Time in five seconds. New tracing by Kruse, Heidt, and Stewart.

Strophanthin perfused through the isolated heart by the method of Bock produces little or no change in rate, but the volume of the beat is increased sufficiently to slightly raise the pressure. The toxic margin is very slight in this case, and in the toxic stage the heart becomes arrhythmic, the muscles fibrillating, and death follows with the heart in the fibrillation stage.

5. **The mammalian heart in situ.**—We owe largely to Cushny¹ the details of the influence of strophanthin on the mammalian heart studied in its normal position. The therapeutic action of digitalin or of strophanthin produces in the mammalian heart an increase in the systolic phase of the contractions of both the auricles and the ventricles.

As a rule, with the change in amplitude there is a slowing of the heart rate. The individual contractions are more complete, that is, have both a greater amplitude and a greater relaxation, hence the filling and emptying of the heart is more efficient. This efficiency

¹ Cushny, Arthur R.: *Heart*, Vol. IV., p. 33, 1912.

is twofold, i.e., increased diastole, therefore greater filling, and increased systole, therefore more effective discharge. This effect is accomplished by the twofold action of digitalis. (1) The direct muscular action increases the muscular contractions when they occur, and (2) the action of the vagus center holds in check the muscular effects and in the face of the muscular stimulus produces a greater dilation and more efficient filling of the cavities of the heart.

TABLE I

Experiment 1 of Cushny on a dog narcotized by morphine and curare, Myocardiograph attached to the left ventricle.

Time.	Number of contractions in 10 seconds.	Height of systole from base line.	Height of diastole from base line.	Length of excursion of lever.
Normal.....	35	26 mm.	38½ mm.	12½ mm
After 20 seconds.....	35	27 mm.	39 mm.	12 mm.
" 50 "	33	26½ "	43 "	16½ "
" 70 "	28	25 "	45 "	20 "
" 90 "	24½	23 "	44 "	21 "
" 110 "	22	20 "	43½ "	23½ "

The experiment shows slowing of the heart rhythm, with a more complete systole. There is much greater diastolic relaxation, therefore a corresponding increase in the total excursion of the ventricular contractions.

TABLE II

Experiment 9 of Cushny, cat narcotized with morphine and acetone chloroform, atropine to poison the vagus.

	Rate in 10 seconds.	Contraction volume.	Percentage increase in contraction volume.	Output in 10 seconds.	Percentage increase in output per 10 seconds.
Before strophanthin.....	18	23	..	414	..
After strophanthin.....	18	27	17½	486	17½
Later.....	18	29	26	522	26
Still later.....	18	30½	33	549	33

This experiment shows no slowing of the heart; in fact, no change in heart rate, but an increase in the amplitude of the contractions. Therefore the efficiency of the heart is markedly increased by direct action of strophanthin on the muscle walls.

As the therapeutic stage passes toward the toxic stage an interesting intermediate condition supervenes in the heart. The increase in the irritability of the muscle tends to break down the sequence and the rhythm within the heart, while the hyperirritable condition of the vagus center tends to hold the heart in inhibition. There will come at this time periods of quite rapid contractions interspersed with periods of very slow beats or even complete inhibition. The medullary and local nervous centers pass into the paralytic stage somewhat earlier than does the muscle, hence the direct cardiac muscle stimulation presently becomes dominant. More frequent series of rapid beats now occur, with an increase in efficiency of the heart as a pump. However, this condition does not last long, since arrhythmia soon sets in because of the increasing hyperirritability of the muscle. The contractions of the auricle at this stage are not always followed by contractions of the ventricle, nor are these two events in proper sequence.

In addition to the change in irritability of the muscle substance, there is an influence of digitalis on the conducting substances of the bundle of His. There is evidence, chiefly therapeutic, to indicate that digitalis diminishes the rate of conduction through this special mechanism of the mammalian heart. In other words, digitalis in its tendency to produce slowing of the auriculo-ventricular interval accomplishes an effect of more or less complete heart block. The mechanical effect of the combined change in the muscular irritability and the depression of conduction in the bundle of His is a great irregularity in the blood-pressure. When, during the arrhythmia, the auricular and ventricular contractions happen to fall in sequence, there is a sharp rise of blood-pressure; when they are in opposite phase, a similar fall. The ultimate toxic result is increasing arrhythmia, inefficient contractions, fall of blood-pressure, and final paralysis and cardiac death.

6. Digitalis on the peripheral arterioles.—Members of the digitalis series produce a marked contraction of the arterioles throughout the body. This peripheral vascular contraction produces a tremendous increase in the peripheral resistance to the blood flow and a resulting great rise in blood-pressure, which may amount to from 50 to 100 per cent.

The vascular constriction is most pronounced in the visceral organs of the abdominal region. This was especially investigated by Gottlieb and Magnus¹ in 1902. These authors compared the action of the

¹ Gottlieb and Magnus: *Arch. f. Exper. Path. u. Pharm.*, Vol. XLVII., p. 135, 1902.

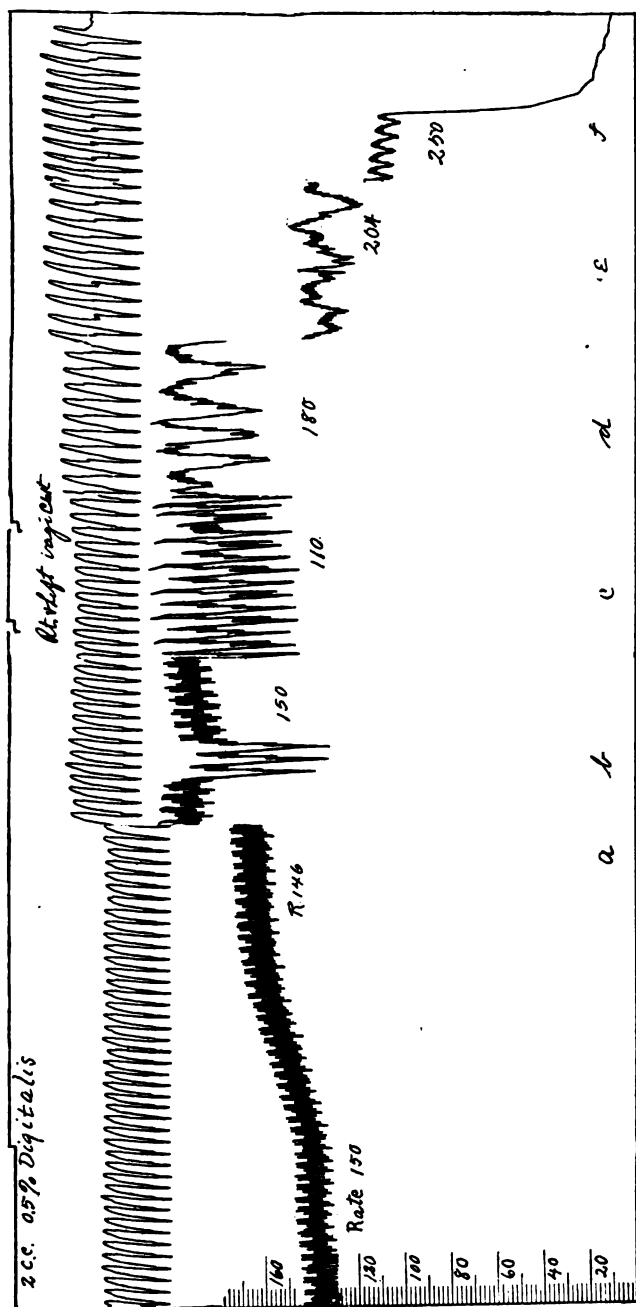


FIG. 55.—The influence of soluble digitalin on blood-pressure and respiration. At the beginning of the tracing 2 cc. of 5 per cent. digitalin was slowly injected into the femoral vein. In the interval between *b* and *c*, and between *d* and *e*, the dose was repeated. In the segment *c* the vagus nerves were cut, producing no immediate change in the blood-pressure or heart rate. The respiratory rhythm is slightly slowed and deepened. Interval between *a* and *b*, 6 minutes. The irregularity in rhythm shown in the third such group, the first one coming 50 seconds before. The time from *b* to *c* is 8 minutes. Only a momentary change in the heart rhythm appeared at the instant the left vagus was cut. Between *c* and *d*, *d* and *e*, and *e* and *f* 10 minutes each. In this tracing the extremely slow and irregular rhythm occasionally seen under digitalis did not appear. The regular but rapid heart rhythm just before the heart stopped beating is often noted, as is also the fact that respiration generally lasts longer than the heart rhythm under the toxic action of digitalis. Blood-pressure scale as shown to the left. Time in seconds. New tracing by Alford and Bullard.

different members of the digitalis series on the visceral organs—the spleen, the intestine, and the kidney, and on the peripheral regions, using the volume of the leg as an index. It was shown that the constriction in the volume of the extremities produced by digitalin, strophanthin, convallaria, etc., produced a tremendous rise of blood-pressure, with vascular spasm of the spleen, kidney, and intestine. With the weaker members of the digitalis series the influence on the



FIG. 56.—The effect of 12 mgr. strophanthin, intravenous, dog. From Gottlieb and Magnus.

blood-vessels of the limbs is very much less than on the visceral organs. A quantity of strophanthin, therapeutically active for the viscera, has practically no direct influence on the blood-vessels of the leg. Gottlieb and Magnus found that the volume of the limb even followed the rise of blood-pressure very closely, a result which they explained as the physiological reflex associated with a condition of increased pressure in the viscera. With digitoxin, on the other hand, the vascular spasm was marked in the vessels of the limb as well as in the visceral organs. When they excluded the abdominal circulation the peripheral arterioles contracted in the face of a rise of blood-pressure.

It may be reiterated, therefore, that the digitalis substances produce marked general arterial constriction, though this effect is less strong in the periphery than it is in the viscera. It is less vigorous with certain members, strophanthin, than with others, for example,

digitoxin. In this connection it must be recalled that these two great vascular regions normally act in physiological opposition under many physiological conditions. Therapeutic quantities of digitalin, strophanthin, etc., which just call forth visceral constriction are apt to be associated with dilation of the blood-vessels of the periphery, a secondary effect called forth through the interactions of the ordinary physiological mechanisms.

The analysis of the vasoconstrictor effects of digitalis was made in part by Gottlieb and Magnus. They isolated the organs studied by them from the central nervous system, and found that the vasoconstriction occurred in practically the same degree as before. Others have shown that after sectioning of the splanchnic nerves a marked diminution in the rise of blood-pressure results. It would seem, therefore, that there is some stimulation of the medullary vasomotor centers, though it may be relatively slight and at times insignificant.

Gottlieb and Magnus did not determine on what part of the peripheral mechanism the digitalis acted. Cushny¹ stated in 1897: "I think the evidence is overwhelming that the rise in pressure in the arteries is to a considerable extent due to action on the muscular walls of the arterioles." This point was finally cleared by Dixon,² who poisoned the terminal vasoconstrictor fibers with apocodeine. Digitalis following this drug still produced vasoconstriction, proving that there was a stimulating action on the smooth muscle in the walls of the blood-vessels.

Very slight, if any, change in the resistance of the pulmonary circulation has been noted with digitalis. There is always a marked diminution in the output of blood flowing from the isolated heart, fed by coronary perfusion. This decrease is attributable to coronary constriction.

7. The action of digitalis on the central nervous axis.—It has already been stated that digitalis produces a sharp rise in the tonic action of the cardiac inhibitory center, the details of which have been presented. The vasomotor center also is stimulated, though apparently in less degree. Other medullary centers show some slight increase in tonic activity, especially the respiratory, as indicated by the change in respiratory rate and depth. Mackenzie states that in clinical treatment "the most frequent nervous symptom was headache," sometimes so severe as to stop the use of the drug. Perfusions of digitalis in experiments on the circulatory system of lower animals with intact

¹ Cushny, A. R.: *Jour. of Exper. Medicine*, Vol. II, pp. 233-313, 1897.

² Dixon: *Jour. of Physiology*, Vol. XXX., p. 97, 1903.

spinal cords are very often accompanied by a marked increase in reflex movements. The same may be observed also on mammals, all showing an increase of the reactions of nerve centers under the influence of the digitalis. Toxic doses of digitalis lead to convulsions which are undoubtedly of central origin. The direct therapeutic effect of digitalis on the cord and medullary portions of the nervous system is that of a general nerve tonic, especially on the vagus nucleus.

8. Digitalis as a diuretic.—Any drug which produces so profound an influence on the circulatory system as digitalis may be expected

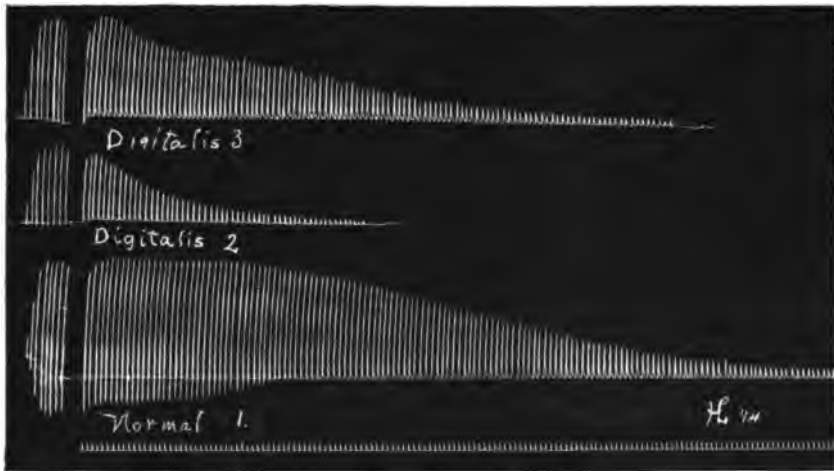


FIG. 57.—The influence of digitalis on the irritability and muscle work of the gastrocnemius of the frog. Tracing No. 1 is from 20 gram. frog, dose 8 minims of 0.1 per cent. solution, allowing 20 minutes for absorption. There is little change in irritability, but the amount of muscle work obtained is markedly diminished. Top tracing No. 2 shows the action of 6 minims of 0.1 per cent. solution on an 18-gram. frog after 15 minutes of absorption. The normal tracing is not shown, but it is very similar to the normal represented. Minute doses of digitalis slightly increase the amount of work given by the gastrocnemius. New tracing by La Force.

to change the functional activity of the kidney. If for no other reason, this effect would occur indirectly from the action of the drug on the circulation. The volume of the circulation through the kidney is often decreased by profound vasoconstriction in the acute stage, but in the general administration of digitalis the total efficiency of renal circulation is raised.

Digitalis produces diuresis. This can be demonstrated on the normal animal, where diuresis is distinct though relatively slight. In pathological conditions, especially when involving the circulatory ap-

paratus associated with dropsy and edema, this diuretic action is very greatly increased.

The mechanism of diuresis by digitalis has been variously explained, by some authors as wholly vascular, by others as due to a direct influence of the drug on the renal epithelium. While one must admit the favorable vascular effects it seems that one cannot deny the direct renal stimulation. In relation to the clinical dropsical condition there is a disturbance of function of the vascular endothelium over the body which varies the regulative control as between the fluids inside the blood-vessels and the fluids in the lymph spaces and in the tissues. Digitalis produces some stimulation of this endothelial tissue, increasing its efficiency of action. It thereby favors the taking up and elimination of the excess of tissue fluids. Similar action also falls on the lining cells of the renal blood-vessels as well as on the renal epithelium.

9. **The local irritating effect of digitalis.**—Digitalis applied locally to mucous membranes or hypodermically injected into the cutaneous or muscular tissues, produces considerable local irritation. This irritation may lead to the usual cycle of inflammatory changes, even to the formation of local abscess. There is a sharp stimulation of the sensory nerve endings, accompanied by acute pains. These facts make it undesirable to administer members of this series hypodermically.

Digitalis, by way of the mouth, when its administration is oft repeated, has a tendency to produce gastric irritation and even inflammation. The nausea and vomiting that occasionally occur after digitalis, or more often after squills, are due to reflexes set up by gastric irritation.

IV.

The Cumulative Action of the Digitalis Series.

The effects of digitalis are very persistent in the body. Absorption of the drug is indeed relatively slow, but its elimination is extremely slow, complete elimination taking place only after many days. The result is that in repeated dosage the effects are additive, i.e., cumulative. Cases of poisoning by digitalis have occurred from the too rapid administration of otherwise therapeutic doses. Digitoxin especially, which is the most toxic of the series, a dose of 2 mg. being dangerous for a grown man, is particularly slow in its elimination, hence cumulative in its action.

The great variation in the strength of digitalis leaves and the preparations made therefrom, together with the fact that the active principles tend to decompose, all require standardization of these drugs by measurement of the reactions on mammals. At the present time most firms are issuing physiologically standardized preparations. The clinician should be particularly careful to use recently standardized preparations, a caution that applies no less to the experimentalist.

V.

Summary of Pharmacological Action.

The members of the digitalis series are extremely toxic, yet because of their almost specific action on the circulatory apparatus they have proven invaluable as therapeutic agencies. Members of the series vary somewhat in their relative intensity of action at different points of the body. In therapeutic quantity the chief changes produced in the body are: Strengthening of the heartbeat and slowing of its rate—strengthening through direct muscular action and slowing through stimulation of the inhibitory nerves, primarily through the inhibitory center in the medulla. There is a sharp and general rise of blood-pressure from arterial constriction, the effect being produced primarily by direct stimulation of the muscles of the arteries, but in some degree by similar stimulation of the vasomotor center. The arterial constriction is greatest in the splanchnic region, in mild doses being almost limited to this area. However, vasoconstriction is produced in all parts of the body, especially by the very toxic digitoxin. In toxic dose the inhibitory stimulation of the heart is profound, while the direct increase in muscular irritability tends to produce arrhythmia and delirium cordis. The algebraic sum of these two factors results in great irregularity of blood-pressure in this stage.

The change in the circulation to some extent accounts for the diuretic value of digitalis, though a favorable stimulating effect upon the renal epithelium is to be assumed. Digitalis produces local irritation of the mucous membranes. Acute sensory stimulations, also inflammatory changes, occur in the local area when digitalis is given hypodermically. The inflammation is accompanied by the usual vascular congestion, edema, and sometimes degeneration of the tissue with pus formation. The sensory stimulations lead to important reflex effects, also to acute pain. Local irritation in the

stomach produces nausea and vomiting. Toxic doses induce central nervous spasms ending in paralysis.

The digitalis substances act cumulatively, due to their extremely slow elimination from the body. Excretion occurs chiefly through the kidney. In the present state of our knowledge of the chemistry of the active principles of this group clinicians must rely upon physiological standardization of these products.

BUFONINE AND BUFOTALINE.

I.

Historical and Chemical.

Faust¹ (1902) isolated and identified two digitalis-like principles from the skin of the common toad. It was known in ancient times that the dried skin of the toad possessed certain toxic properties and this material entered into the list of medicinal substances. Bufonine possesses the formula $C_{28}H_{44}O_2$, and bufotaline, $C_{28}H_{44}O_{1.5}$. They are not glucosides but are chemically related to cholesterol.

These substances are of peculiar interest because of their animal origin.

II.

Pharmacological Action.

When injected subcutaneously or given by way of the mouth they produce digitalis-like changes in the functions of the animal tested.

1. **On the frog's heart.**—Bufotaline produces on the frog's heart a marked slowing of the rate and an increase of the pulse volume.

2. **On the mammal.**—Subcutaneously a 2.6 mgr. dose produced in the dog increased secretions and evidences of nausea followed by vomiting. There is a decrease in the rate and amplitude of respiration with Cheyne Stokes breathing. The heart is very irregular, the pulse small and strong. Similar phenomena occur in rabbits, but as the experiment proceeds there is a distinct dyspnea as with digitoxin. In the toxic stage convulsions occur.

3. **On blood-pressure and the pulse.**—On mammals bufotaline produces a decrease in the pulse frequency with an increase in the pulse volume.

Bufonine produces the same qualitative physiological effects as bufotaline, but is much weaker in its action.

¹ Faust, Edwin S.: *Archiv f. Path. u. Pharm.*, Vol. XLVII., p. 278, 1902.

CHAPTER XXI.

THE SAPONIN AND SAPOTOXIN GROUP.

I.

Historical and Chemical.

Saponin and sapotoxin are widely distributed and highly toxic glucosidal principles. They are pharmacologically classified with the protoplasmic poisons, but are inserted here because chemically they are non-nitrogenous and in decomposition yield glucose. They are of the general chemical composition $C_nH_{2n} = .O_{10}$ (Kobert).

Of the plants yielding members of the group may be mentioned as most important

The Soapbark, *Quillaja saponaria*
The Soapwort, *Saponaria officinalis*
Sarsaparilla, *Smilax*
The Corncockle, *Agrostemma githago*

Closely related to the Saponins are the Solanins, which are glucosidal alkaloids yielded by the black nightshade, bitter sweet, potato, etc., members of the species *Solanum*. Solanin is decomposed into a glucose and a poisonous base, solanidin. Solanin is present in the green and growing parts of the potato, sometimes in quantities sufficient to produce distinct poisonous symptoms. Saponin is very much less toxic than sapotoxin.

II.

Details of Pharmacological Action.

Members of the saponin series are chiefly of toxicological interest. They are toxic to practically all the tissues. Their property of forming emulsions adapts them to commercial use to cleanse substances that are injured with the alkalis. For example, soapbark enjoys a well-merited popularity as a hair wash.

1. **Sapotoxin as an irritant.**—Sapotoxin is a violent local irritant. When inhaled this action on the nasal epithelium leads to uncontrollable reflex sneezing. The local inflammation thus produced may under certain conditions prove decidedly injurious.

Hypodermic injections also lead to inflammation at the point of injection.

When introduced into the stomach sapotoxin produces the usual cycle of events following gastric irritation, namely, pain, nausea, and vomiting. As absorption does not readily occur systemic effects may not follow these local gastric changes.

2. **Toxic systemic effects.**—The toxic symptoms produced by the sapotoxins are in large part due to the irritant nature of the drug. There is in

the mild stages general *malaise*, loss of appetite, often with vomiting and diarrhea, feeble pulse, and respiration, leading in the stronger action to convulsions and respiratory failure. The tissues throughout the body show more or less evidence of inflammation and disintegration, especially the capillaries whose walls are often permeated, showing hemorrhagic extravasation. The hemoglobin is discharged from the blood by the hemolytic action of the saponins, a reaction which also takes place in the test tube. The explanation of the hemolysis is that the saponins dissolve the fat-like material in the wall of the corpuscle.

3. **Saponin.**—Loeb and Wasteneys¹ have reported experiments showing that the cytolytic action of saponin on the cortical layer of the eggs of the sea urchin tends to increase the rate of oxidation under certain conditions. They give the following table as an example:

TABLE I

Eggs of <i>S. Purpuratus</i> , Temp. 15°C.	Oxygen consumed per hour	Coefficient of rate of oxidations.
	Mgr.	
Unfertilized eggs.	0.15	1.00
The same eggs after cytolysis with saponin.....	1.07	7.10
Unfertilized eggs.....	0.22	1.00
The same eggs after cytolysis with saponin.....	0.80	3.60

"The variation in the effects of cytolysis in the two experiments may be due to the fact that in the second experiment an excessive amount of saponin was used.

"This experiment proves that the increase in the rate of oxidations due to fertilization or artificial membrane formation is merely caused by the cytolysis of the cortical layer."

4. **Solanin.**—The potato poison, solanin, has the same general toxic action as saponin and requires no special discussion.

¹ Loeb, J., and Wasteneys, H.: *The Journal of Biological Chemistry*, Vol. XIV., p. 479, 1913.

F. *Drugs, Chiefly Alkaloids That Primarily Influence General Metabolism.*

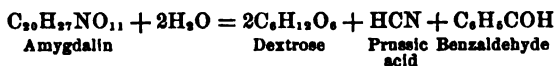
CHAPTER XXII.

HYDROCYANIC ACID.

I.

Chemical.

Hydrocyanic acid and the cyanides are very toxic substances which owe their physiological action to the *CN* group, cyanogen. This group is represented in nature in certain animal secretions and in certain plant products. It is present in the seed of the bitter almond in the compound known as amygdalin. When amygdalin is decomposed by the natural ferments it sets free hydrocyanic acid or prussic acid. The bitter almond kernel yields about one-fourth of one per cent. of hydrocyanic acid, according to the reaction:



The inorganic salts, the cyanides, in solution, yield the active cyanogen ions. The most common of the salts used in experimentation and in medicine are sodium cyanide and potassium cyanide.

II.

Outline of Pharmacological Action.

1. *Toxic to protoplasm, especially to nervous tissue, which it paralyzes after an initial stimulation, the respiratory center being the vulnerable point.*
2. *Destructive to enzyme action.*

III.

Details of Pharmacological Action.

1. **On the central nervous system.**—Prussic acid is especially toxic to animal tissues and particularly to the delicately sensitive

nerve tissues. Its toxicity is undoubtedly due to interference with oxidations, a deduction that is strengthened by the experiments of Loeb on general protoplasm. Loeb¹ has found that potassium cyanide inhibits the oxidation processes in the protoplasm of the ova of certain invertebrates.

On nerve tissues of all kinds the cyanides at first increase the irritability, then depress and paralyze. Particularly on the centers of the medulla does this change show itself. These centers have their reflex irritability greatly increased at first, then rather quickly follows a marked depression to the point of complete loss of irritability. The cycle of changes is not unlike that of asphyxiation, a phenomenon that is indeed involved. The nervous centers controlling respiration, the glands, the eye, and the vascular mechanisms, are all at first stimulated then rapidly depressed, all in a few seconds in the presence of toxic doses. These changes are of themselves largely sufficient to explain the cycle of symptoms which occur on the administration of prussic acid and the cyanogen compounds.

2. On respiration.—The action of the cyanides on the respiratory center is so striking and so important that it calls for special mention. Under the cyanide influence the discharges from the respiratory center are greatly strengthened and markedly accelerated. These changes are followed by respiratory depression to the point of complete standstill. The ganglion cells of the respiratory center are directly altered by the cyanides in such manner as to prevent the utilization of oxygen. In therapeutic quantity hydrocyanic acid is therefore a respiratory stimulant. Dresser² showed that 0.6 mgr. potassium cyanide produced in the rabbit both an acceleration of respiratory rate and an increase in the expiratory volume. His experiment is as follows:

RABBIT (weight 2170 grs., under 1.6 grms. urethan, vagi sectioned).

	Expiratory volume.	Frequency per minute.
Normal.....	156 cc.	80
After 0.0006 grm. KCN.....	175 cc.	82

In toxic quantity, and cyanogen is very toxic, it quickly leads to loss of medullary respiratory control, and death follows from

¹ Loeb, Jacques: *Biochemische Zeitschrift*, Vol. XXVI., p. 279, 1910.

² Dresser, H.: *Archiv f. Exper. Pathol. u. Pharmacol.*, Vol. XXVI., p. 237, 1890.

asphyxiation of the tissue. The stage of depression can be greatly alleviated and sometimes recovered from by artificial respiration, since the tissues are not directly so strongly influenced toxicologically as are the nervous reflexes involved.

3. On the circulatory system.—Changes occur in the circulation at three points, i.e., the peripheral blood-vessels, in the heart, and in the controlling nerve centers. Using isolated organs (the kidney) Sollmann has shown a vascular dilation when solutions of hydrocyanic acid gas were perfused. When the normal solutions were substituted there was a disappearance of the dilation of the blood-vessels.

The heart is directly influenced by this drug. Loewi¹ has shown that .00013 per cent. hydrocyanic acid is sufficient to partially depress the pulse frequency, while .00025 per cent. rapidly lowers the amplitude of contraction. Prolonged contact of the cyanides is especially depressing to the heart function, presumably by interference with the oxidation processes.

The chief cardiac change, however, is due to the influence of the cyanides on the central nervous system. The vagus center is at first stimulated, leading to cardiac slowing by vagus inhibition. In a similar manner the vasomotor center shows an initial stage of increased tone, followed by depression of function as toxicity appears.

When perfused through the isolated frog's heart hydrocyanic acid or its compounds quickly produces a cessation of the rhythm, the heart stopping in diastole. The irritability of heart muscle, although depressed, is not completely lost for a time, as can be proven by applying stimulating electrodes directly to the muscle. Recovery with the perfusion of normal fluids is relatively rapid.

4. On metabolism.—It is evident that a substance so toxic as a cyanide will influence the metabolism of protoplasm in general. This is true in this case. The CN group, by interfering with oxidations, depresses metabolism. This is proven by experiments on both animals and plants. Animals show a decrease in the percentage of oxygen consumed and carbon dioxide liberated, further proof indicating a decrease in the oxidative processes (Geppert).

There is some evidence that the cyanides take part in the reactions occurring in certain normal functions of the tissue. One such evidence is found in the presence of sulpho-cyanides in the saliva. Then, too, prussic acid is eliminated from the body in the form of sulpho-cyanides.

Prussic acid produces cyan-methemoglobin in the body, a reac-

¹ Loewi, Otto: *Archiv f. Pathol. u. Pharm.*, Vol. XXXVIII., p. 126, 1897.

tion that is especially characteristic when the reagent is mixed with blood in the test tube. This compound is a combination between the hematin and the hydrocyanic acid. In cases of poisoning from this drug the blood of the animal possesses a bright red color, which is characteristic. The reaction between methemoglobin and hydrocyanic acid is characteristic and extremely sensitive. If a sample of blood have added potassium chlorate to produce methemoglobin, and a drop of this fluid be allowed to spread on a filter paper, then the merest trace of hydrocyanic acid in a suspected solution when added to this methemoglobin paper will produce a change in color from the dark brown-red to a brilliant scarlet-red.

CHAPTER XXIII.

ACONITE.

I.

Historical and Chemical.

Aconite, from the roots of monkshood, *Aconitum napellus*, is one of the most toxic, and at the same time one of the oldest known poisons. The active alkaloid, aconitine, presents some difficulties in its isolation because of the readiness with which it decomposes. The related alkaloids of this group are found in species of the genus *Aconitum*, from which are derived aconitine, with the chemical formula, $C_{34}H_{47}NO_{11}$; pseudoaconitine, $C_{36}H_{49}NO_{12}$; delphinine, $C_{31}H_{49}NO_7$.¹ The last named drug is less toxic than the first.

On hydration aconitine and its relatives break down into acetic acid and benzaconine. The latter further decomposes into aconine and benzoic acid. Because of the ease of cleavage of aconitine there is in its commercial preparations great variation in the proportion of the different cleavage products. This presents an element of danger, as is obvious, considering the toxicity of the alkaloid, the fatal dose for man being 3 mgr.

II.

Outline of Pharmacological Action.

1. *Aconite is a general protoplasmic poison of extreme toxicity.*
2. *Like many poisons, it at first stimulates, then paralyzes the tissue. Aconite is particularly poisonous to the basic centers of the central nervous system.*
3. *It produces primary sensory stimulation followed by paralysis.*
4. *The blood-pressure is depressed by vasodilation and by slowing of the heart through primary stimulation of the vagus center.*
5. *Heart muscle, as such, is stimulated, and is finally set into fibrillation by toxic doses.*

¹ These formulæ are those presented by Schmiedeberg's *Pharmakologie*, 6th edition.

III.

Details of Pharmacological Action.

1. **Systemic action.**—Aconite in toxic quantity, 2 or 3 mgr. for man, produces almost immediate paralysis of the medullary centers, with respiratory and cardiac failure. In therapeutic quantities there is a primary medullary stimulation of the cardiac inhibitory center (questioned by Mackenzie recently), but with depression of the respiratory mechanism. The sensory symptoms are also most characteristic. After absorption there is a stinging, prickling, or tingling sensation of the skin. If the drug is taken by the mouth, this local effect appears first in the mouth, tongue, and throat. If these first symptoms are rather severe they are apt to be followed by a feeling of numbness from incipient local sensory paralysis. Aconite is rather readily absorbed, and when applied locally to the skin or to mucous surfaces it leads to the same local sensory symptoms as when taken internally. Stimulation by local action produces marked reflexes which influence the different fundamental tissues according to the point at which the local stimulation is produced, i.e., insalivation, gastric irritation, with nausea and oftentimes vomiting.

The fact that the peripheral sensory effects are produced by aconite after absorption, is generally explained on the ground that the stimulation and paralysis occur in the peripheral structures. Aconite apparently produces a somewhat selective paralysis of cutaneous sensory mechanisms.

2. **Aconite on the central nervous system.**—The primary action of aconite on the central nervous system is that of mild initial stimulation, followed by depression and paralysis. This is true especially for the medullary and spinal centers. Slight, if any, effect is noted on the cortical region, since consciousness remains intact until death. Of the medullary centers the chief symptoms of stimulation are noted in connection with the cardiac inhibitory center and the vasomotor center. The cardiac inhibitory center is primarily stimulated, as shown by slowing of the heartbeat. In the same way the vasomotor stimulation is indicated by peripheral vascular constriction. The respiratory center is mildly stimulated, then the amplitude is depressed and the movements slowed, a condition which is succeeded by ultimate paralysis and death by asphyxiation.

3. **Aconite on the circulatory system.**—The circulatory influences of aconite are twofold, i.e., cardiac and vasomotor. When the drug

is injected intravenously into the circulatory apparatus of a normal animal, for example, a frog or a mammal, the heart is at first accelerated, then greatly slowed, often stopped. Still later this is followed by a series of weak beats or sometimes by complete quiet. This contradictory picture is explained by the successive stimulations, which occur on different parts of the cardiac mechanism. The stimu-

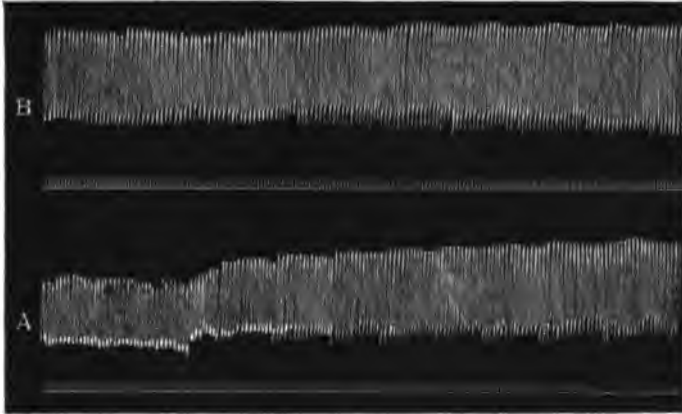


FIG. 58.—The stimulating action of .001 per cent. aconite on the contractions of the frog's heart. This concentration ultimately leads to arrhythmia, but the immediate effect is a great increase in the contraction. A, first perfusion; B, second perfusion after several minutes' interval. Time in seconds.

lating effects of the aconite fall on the medullary centers, the nerve endings in the muscle, and on the muscle itself. In the first or acceleration stage the accelerator nerve endings are dominant; in the stage of slowing and inhibition the inhibitory nervous apparatus is dominant. After the regulative nerves are finally paralyzed the fundamental rhythmic property of the muscle is free to act, and the heart is able to carry on beats for a time. The automatic rhythm finally ceases. However, the muscle can still be made to contract by direct electrical stimulation, though this power does not last long.

The direct action of aconite on isolated cardiac muscle is primarily stimulating, producing an increase in the rhythm, followed by incoördination and later by paralysis. When the rhythm has disappeared, the muscle can be made to contract by the direct application of a strong electrical stimulus. Cushny¹ has recently examined the

¹ Cushny, Arthur R.: "The Irregularities of the Mammalian Heart Observed under Aconitine and on Electrical Stimulation," *Heart*, Vol. I., pp. 1-22, 1909.

reactions of the mammalian heart and finds that there is marked interference, both with the conduction of the contraction wave and with the rhythm. The mammalian heart in an early toxic stage shows in a large percentage of the cases reversal of sequence, i.e., to the ventricle-auricle rhythm, in which the impulse is "generated in the ventricle and spreads upward to the auricle." He finds an impaired conduction, which may at times lead to partial or complete block. There is also a tendency to "sudden changes in the rhythm of the whole heart. It is evident that aconite produces a profound change, not only in contractility, but in rhythm and conductivity in the mammalian heart."

4. **Aconite on the blood-vessels.**—The exhibition of aconite causes an initial contraction of the blood-vessels, from the stimulating action of the drug on the vasomotor center. This stage of stimulation, however, is very brief, and later, as the nerve center becomes depressed vasodilations occur, as shown by slight flushing of the skin. In the therapeutic action of aconite on the circulatory system, therefore, the great inhibitory slowing of the heart, together with the tendency to vascular dilation, leads to a general fall of blood-pressure, with depression of the circulation as a whole, a condition which undoubtedly enters into the antipyretic action of the drug.

5. **On the glands.**—An increase in the secretion of the glands of the mouth and especially of the skin is noted after aconite. But the increased flow of saliva is primarily reflex, due to stimulation of sensory endings in the mouth. However, some stimulation of the secretory center in the medulla may also occur.

6. **Aconite as an antipyretic.**—Aconite because of its great toxicity to protoplasm tends to lower the metabolic processes of the body. In fevers, which result from increased central stimulation, aconite is particularly effective, and lowers the temperature by depressing metabolism. The lowering of heat production is added to the increased heat loss from the dilation of the cutaneous blood-vessels and the increased secretion of perspiration mentioned above, hence the general body temperature is brought down. To what extent this action falls on the heat regulating centers of the brain is not fully explained.

IV.

Summary of Pharmacological Action.

Aconite is the most toxic of alkaloids and is poisonous to all the tissues of the body. Its action is characterized by an initial irritative or stimulative process, followed by loss of function or by paralysis. In the central nervous system the cortex is not particularly affected, but the vital centers of the brain-stem and cord are especially poisoned. The cardiac inhibitory, the vasomotor, and the secretory centers of the medulla are initially stimulated, then with the respiratory center, depressed and paralyzed. Of these influences the stimulation of the respiration is practically negligible, while that of the inhibitory center is strong. Death follows from the cessation of respiration and by paralysis of the heart.

The most characteristic, one might almost say specific, influence of aconite is on the sensory receptive organs. Cutaneous sense organs are stimulated by the smaller doses, which may reach them either locally or through the circulation. Here, too, stimulation is followed by depression and paralysis. On peripheral tissues, the glands, skeletal muscles, heart muscle, and smooth muscle, aconite exerts a rather strong initial stimulation, though in each tissue ultimate paralysis follows.

The general effect on metabolism is to lower heat production. Dilation of the blood-vessels of the skin and the greater evaporation of sweat increase heat dissipation, hence contribute to the general lowering of temperature. The former use of aconite as an antifebric is falling into disrepute because of the danger from its depressant cardiac action. Aconite is being displaced by safer antipyretics which are now available.

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CHAPTER XXIV.

VERATRINE.

I.

Historical and Chemical.

Veratrine is representative of a series of very toxic alkaloids closely related to aconite and derived from different species of Lilaceæ. The most important is veratrine, $C_{32}H_{49}NO_9$, from *Veratrum sabadilla* and *Veratrum viride*, and protoveratrine, $C_{32}H_{51}NO_{11}$, from *Veratrum album*.

Aside from these there are some eight or ten related alkaloids which have been isolated and most of them tested pharmacologically.

The name Hellebore, sometimes used, confuses the above plants with *Helleborus niger*. Helleborine, the active principle of the latter plant, is classified in the digitalis series, to which it is most closely related. The alkaloid of the death Camas, the poisonous lily of the valleys of the Cascade Mountains, contains members of this series, as demonstrated by Slade¹ in 1905.

II.

Outline of Pharmacological Action.

1. *The chief action of the veratrine alkaloids is due to their extreme general toxicity, but they possess a degree of selective activity on sense organs and sensory nerves and on muscle substance.*

2. *A peculiar and typical stimulation of muscular contraction leads to persistence of the muscular tone and delayed relaxation.*

III.

Details of Pharmacological Action.

1. **Veratrine on sensory and nervous mechanisms.**—Like aconite, veratrine causes a pronounced stimulation of sensory organs, especially the cutaneous sense organs. This occurs whether the drug be taken systemically or brought into contact with the tissues locally. The symptoms are smarting and tingling, and peculiar temperature-

¹ Slade: *American Journal of Pharmacy*, Vol. LXXVII., p. 262, 1905.

like sensations, followed by anesthesia of the skin. On the nasal mucous membrane it leads to irritation, with reflex stimulation, sneezing, coughing, etc. In the mouth the sensations are those of burning and stinging pain, with slight involvement of taste sensations. All of these symptoms are followed by anesthesia in the later stage of action.

Veratrine is extremely toxic to nerve tissues. Yet under certain conditions of hyperirritability of these systems veratrine is truly antidotal.

2. Veratrine on skeletal muscle.—Pharmacologically the action of veratrine on skeletal muscle is most interesting. All kinds of muscular tissues are affected by the alkaloid, and in much the same way in the various species of animals.

Isolated skeletal muscle contracts in the normal way after veratrine, but relaxation is extraordinarily prolonged, many times that of the normal relaxation. This effect is characteristic. When the poison is given systemically the inability of the skeletal muscles to quickly relax leads to a peculiar type of general muscular movement in the poisoned animal. Such animals can make quick enough muscular contractions, as in the limb extensions in leaping, but the return to the normal relaxed position is hindered. This leads to very irregular and seemingly incoördinated movements, and to the fixing of the body in the position of contraction of the stronger sets of muscles.

The explanation offered of this veratrine effect, which has received most general consideration, is that of Bottazzi.¹ This author, in 1901, called attention to the double nature of skeletal muscle substance, namely, that it possesses highly differentiated fibrillæ surrounded by a certain amount of less differentiated sarcoplasm. The fibrillæ are responsible for the characteristic quick contractions of skeletal muscle, in which the part taken by the sarcoplasm is slight and thrown into the background. Under the influence of veratrine (and the effect is produced by other muscle poisons, such as muscarine, helleborine, etc.), the irritability of the sarcoplasm is sharply raised. When a muscle receives a single stimulus, such as calls forth a typical simple contraction, the fibrillæ respond with the usual rapidity, and the contraction phase is as short and abrupt as in the normal. Relaxation begins in the usual way, but before it proceeds far is arrested by the slowly developed second contraction, and is followed by a very prolonged relaxation. The delayed relaxation is by this view

¹ Bottazzi: *Arch. f. Physiologie*, p. 377, 1901.

due to the stronger contraction of the slower reacting sarcoplasm, which develops under the influence of veratrine. The recorded tracing is the algebraic sum of the contractions of the two substances, i.e., the quick contraction of the fibrillæ and the slower but hyper-stimulated contraction of the sarcoplasm.

By the above theory it is obvious that the prolongation effect will be greater in those tissues which have relatively greater amounts of sarcoplasm. This is found to be the case. The effect is more pronounced in the order—smooth, cardiac, skeletal muscle. Certain animals whose muscles of a given type are known to possess a relatively

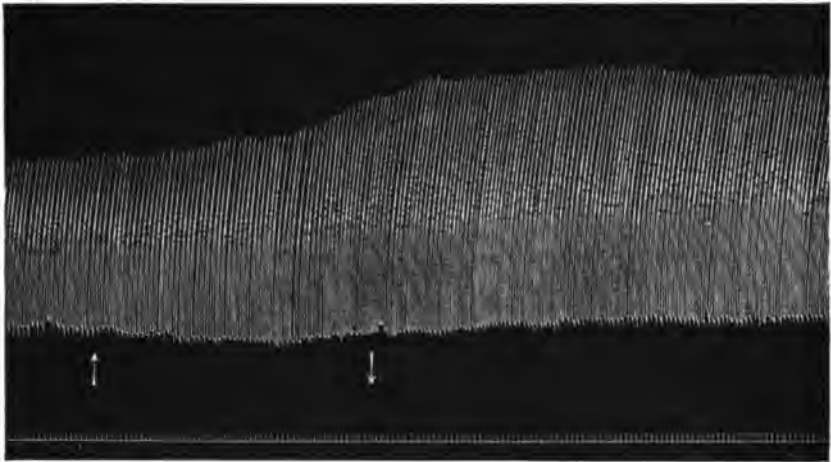


FIG. 59.—The influence of veratrine, 0.0002 per cent. in Ringer-blood perfused through the coronary vessels of the cat heart, between the two arrows. There is a slight delay in the effect represented by the time the fluid is flowing through the cannula. Just before the second arrow, the lever misses at the top an amount indicated by the dotted line. New tracing by Bullard and Stine.

greater amount of sarcoplasm respond even more characteristically, as, for example, in the muscular tissues of the toad.

3. **Veratrine on the heart muscle.**—Heart muscle, as has already been stated, is influenced by veratrine in that the contractions are also prolonged and the relaxations delayed, a phenomenon shown most typically in the cold-blooded animals. The heart muscle tends to persist in a continuous contraction in the systolic phase. The heart of the mammal is similarly influenced, though the picture is complicated by a primary stimulation of the nerve fibers of the inhibitory apparatus. Even in the isolated mammalian heart this later stimulation produces a slowing at the beginning of the veratrine action.

4. On smooth muscle.—Smooth muscle is strongly stimulated by veratrine, leading to increase in tone, with persistent contractions in organs where this type of muscle is dominant, i.e., the alimentary canal, the uro-genital system, the peripheral blood-vessels, etc.

Veratrine, like aconite, is a dangerously toxic drug. The therapeutic effects, for which it was formerly used, are now produced more safely by other less toxic substances, hence the practical use of veratrine has declined. It serves, however, through its muscular effects as one of our best pharmacological illustrations of characteristic and specific acting drugs.

CHAPTER XXV.

COLCHICINE.

I.

Historical and Chemical.

Preparations of *Colchicum autumnale* have enjoyed a certain amount of popularity in the treatment of gout, though such treatment has not been based on any pharmacologically demonstrated activities. This plant yields two alkaloids, colchicine, $C_{22}H_{25}NO_6$, and colchicein, $C_{21}H_{25}NO_6$.

II.

Details of Pharmacological Action.

1. **General systemic and toxic effects.**—Colchicine when given in therapeutic quantity produces little or no acute effects, but in stronger dose symptoms follow similar to those of aconite, and to some extent of pilocarpine. There is a slight increase in glandular and muscular activity, with evidences of sense-organ stimulation. These reactions are followed rather late by marked disturbances of the alimentary tract associated with violent pains, vomiting, and diarrhea. Continued therapeutic use leads to gastro-intestinal disturbance. Death is due to collapse of the respiratory system.

The delay in the reaction of the body to colchicine is due to the fact that the real poisonous effects come only after oxidation of the alkaloid into an oxy-produce.

2. **Colchicine on the white blood corpuscles.**—An action which should be mentioned and which can readily be experimentally demonstrated is the production by colchicine of a marked leucocytosis. The immediate effect is a decrease in the number of leucocytes, chiefly polymorphs in the blood stream. This acute effect is followed later by a marked increase. It would seem as though the alkaloid was sharply stimulative to this more undifferentiated cellular type. If leucocytes are stimulated then in all probability the endothelial,

lymphoid, and synovial tissues, and the relatively undifferentiated connective tissues are also similarly stimulated. The stimulation of such tissues finds expression in cell growth and cell multiplication. However, and probably more important clinically, all such tissues as the endothelial tissues of the blood-vessels in reacting to stimulative agencies display first of all an increase in tonic resistance, a strengthening of the factors of control as displayed in their influence on osmotic and exudative processes. One must remember that such tissues form the boundary walls of cavities filled with fluids. It is suggested that this may be the explanation of the beneficial effect observed in the clinical use of colchicum in rheumatism, gout, etc.

CHAPTER XXVI.

EMETINE.

I.

Historical and Chemical.

Emetine, $C_{14}H_{18}CH_2NO_2$, derived from the root of *Cephælis Ipecacuanha*, is noted for its action as an expectorant and emetic.

This alkaloid, too, is a general protoplasmic toxic substance and is to be classed with the aconite group.

II.

Details of Pharmacological Action.

1. **Systemic actions.**—Emetine differs slightly from the other members of the group in its excessive toxic and local irritation. It is this property which, upon its administration, leads to marked irritation and stimulation of the mucous membrane of the mouth, throat, and stomach. In this way it quickly produces reflex nausea, with vomiting, and the train of associated symptoms.

Ipecacuanha, as an expectorant and emetic, possesses the same dangers as have already been strongly emphasized in association with the other members of this series.

G. *Drugs Poisonous to General Protoplasm.*

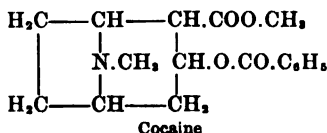
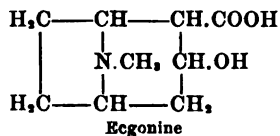
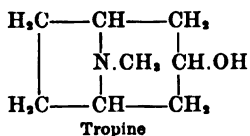
CHAPTER XXVII.

COCAINE.

I.

Historical and Chemical.

The tree *Erythroxylon coca* is native to the Andes of the western coast of South America. The natives conducting the pack trains going through the mountain passes, chew the leaves of this species, in lieu of food, on their long mountain marches. They are said to go for extra long periods without rest or food under these conditions, endurance being greatly increased by the action of the active principle of the Coca leaves, cocaine. Cocaine was made known by Niemann, but its present popularity arose only after its introduction into use as a general local anesthetic in 1884 by Koller. Chemically cocaine is an alkaloid with the composition $C_{17}H_{21}NO_4$. It is a methyl-benzo-ecgonine compound decomposing into ecgonine, pyridine, and benzoic acid.



Ecgonine has a close relationship to tropine which is a hydrolytic cleavage product of atropine. The anesthetic action of cocaine is lost by the removal of the methyl group or of the acid radicle. Other alkaloids are present in small quantities in the species of this genus. These alkaloids owe their toxicity and action to the same base, ecgonine, but differ somewhat in the attached acid radicles.

The most important of these alkaloids is tropacocaine, extracted from the Java Coca.

II.

Outline of Pharmacological Action.

Cocaine is described as a general protoplasmic poison. Its action may be summarized as follows:

1. *Initial stimulation with later anesthesia of nerve tissues. Sensory nerves and sensory nerve endings are peculiarly susceptible.*
2. *Local applications lead to local anesthesia, an effect which readily passes away when the concentration of the drug is sufficiently reduced by diffusion or absorption.*
3. *The central nervous system is at first stimulated, then paralyzed, chiefly in the descending direction.*
4. *Stimulation followed by paralysis of the heart muscle.*
5. *Marked vasoconstriction by central vasomotor stimulation and by peripheral stimulation of the muscles of the blood-vessels.*
6. *Increase in the muscular power and endurance of the skeletal muscle by direct action on the muscle fibers.*
7. *Marked mydriasis.*

III.

Details of Pharmacological Action.

1. **On the central nervous system.**—Cocaine is a recognized excitant of the cerebral cortex and the central nervous system. The excitement stage is associated with increased excitability of the cortex accompanied by restlessness, often passing into convulsions in the toxic stage, and ultimately ending in paralysis. The medullary centers are excited, then depressed, shown in the quicker respiration, the slower heartbeat due to central vagus stimulation, and an increase in tone of the vasomotor center. All these stages pass rapidly into depression and paralysis. The spinal cord, after cocaine, likewise exhibits an increase in the irritability of the motor side of that apparatus. Reflexes are therefore increased, and this is true, not only for the cord reflexes, but for those reflexes which take place through the brain-stem, and even through the cortex itself. The change in function is due to an increase in the sensitiveness of the nervous elements. Dixon has determined that the amount of cocaine necessary to produce convulsions in the different species of animals

closely corresponds to the proportional amount of brain matter per kilo, as indicated in the following table:

	Grams of brain per kilo of animal.	Dose of cocaine per kilo necessary to produce convulsion.
Rabbit.....	4	0.18
Guinea-pig.....	7	0.07
Pigeon.....	8	0.06
Dog.....	9	0.02
Ape.....	18	0.012

Ott found also a strongly toxic influence on the posterior columns of the cord, indicating a slight degree of differential action within the cord.

2. Cocaine on the circulatory system.—The initial effect of cocaine when injected into the circulation is a rise of blood-pressure.

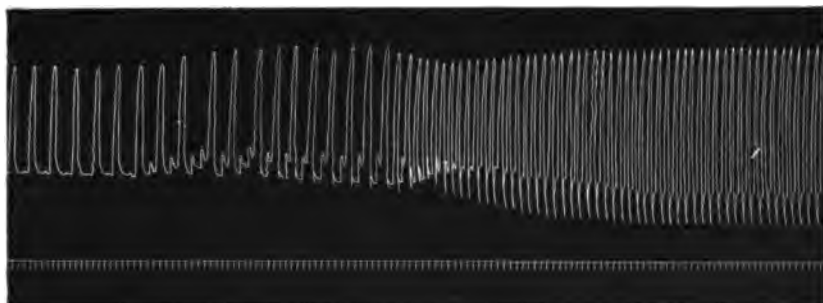


FIG. 60.—The recovery phase of the frog's heart from the depressing action of cocaine. New tracing by Kruse.

This rise is due primarily to great vasomotor constriction, but in part to direct heart effects. The initial rise of pressure is generally followed by a rather sudden fall with a second rise as toxicity approaches. In the toxic stages blood-pressure falls and the animal becomes markedly cyanotic. The variations in blood-pressure may be analyzed by considering the action of the drug on the different parts of the mechanism.

3. The peripheral blood-vessels.—The most striking influence of cocaine is expressed in vasoconstriction. This is sharp, vigorous, and prolonged. The primary rise of blood-pressure is undoubtedly due to the stimulation of the vasomotor center in the medulla. There

is, however, a marked vasoconstriction both in the spinal animal, and in organs for which the vasoconstrictor nerves are severed. Hence the cocaine effect is peripheral as well as central. The peripheral effects are due in part only to stimulation of the nerve endings. Evidence in this direction is the fact that when there is a sharp rise of blood-pressure under the influence of cocaine injection, cutting the splanchnic nerves leads to a decrease of the pressure. The stronger solutions certainly stimulate the muscles of the blood-vessel walls directly, as observed in the blanching of the gums when cocaine is injected for dental purposes.

4. Cocaine on the heart.—The intravenous injection of mild doses of cocaine leads to a marked slowing of the heart, occasionally after a short initial acceleration. This slowing is produced by the stimulation of the inhibitory center in the medulla. Cocaine perfused through the isolated heart of the frog produces little change in rate, but a marked increase in the amplitude of contractions. This indicates a direct stimulation of the contraction amplitude of the cardiac muscle substance. This fact is further confirmed by the influence of cocaine on isolated terrapin heart strips in which also there is a marked increase in amplitude. The isolated mammalian heart gives evidence of direct stimulation of the heart by cocaine in therapeutic concentration, i.e., under 0.0002 per cent. concentration in perfusion fluids.

In all heart work, whether it be muscle or nerve involved, the toxic end effect of cocaine is paralysis and loss of function.

5. Cocaine on skeletal muscle.—As is shown by the practice of the South American natives, cocaine increases the efficiency of the neuro-muscular apparatus in the production of voluntary muscular work. Especially does this effect follow under conditions of fatigue and partial exhaustion.

An analysis of this effect would lead one to suspect that it was due, primarily, to the heightened irritability of the motor nervous mechanism. Experiments on the irritability of the spinal cord indicate that this is a factor. When the isolated gastrocnemius muscle contracting under repeated electrical stimulation is under the influence of cocaine the amount of energy expended is much greater and the onset of muscular fatigue is strikingly delayed. Both these effects in this experiment are to be attributed to the direct action of cocaine on skeletal muscle substance. The functional influence is indeed quite similar to that on cardiac muscle. It is this double favorable therapeutic influence of cocaine on the nerve and on the muscle which

leads to the feeling of freshness and strength under its influence. It is a strong factor in the formation of the cocaine habit.

6. Cocaine on the eye.—One of the toxic symptoms of the influence of cocaine is the dilation of the pupil of the eye. This effect is best studied by the direct application of cocaine into the eye. This leads to dilation of the pupil and a partial loss of accommodation. The dilation of the pupil is not associated with the loss of the light reflex. In other words the oculo-motor nerve is still reflexly active

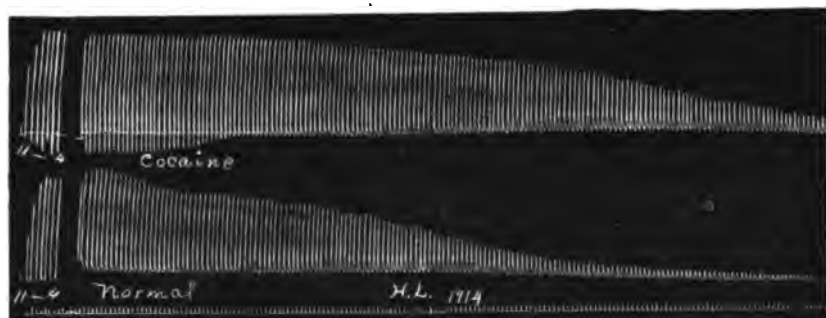


FIG. 61.—Showing the action of cocaine on the amplitude of contraction and the amount of work done by skeletal muscle. The lower tracing represents the work of the normal gastrocnemius of the frog; the upper tracing, the cocaineized muscle. Direct muscle irritability tested in the beginning of the experiment, the cocaineized muscle showing very slightly greater irritability. Four minims of 0.5 per cent. cocaine was injected into the lymph sack 10 minutes before the experiment. Parallel experiments in which the cocaine acts for a longer time show depression on muscle contractility. New tracing by La Force.

in the presence of the local mydriasis. Direct stimulation of this nerve produces active constriction of the pupil. When the superior cervical ganglion is removed cocaine still produces dilation. If, however, the post-ganglionic fibers, Figure 27, page 114, first be allowed to degenerate then the dilation is slight or absent. The whole effect is like that produced normally by stimulation of the cervical sympathetic and is to be attributed chiefly to stimulation of the endings of the post-ganglionic fibers on the radial muscles of the iris.

7. The elimination of cocaine.—Cocaine, like alcohol, is practically all consumed in the body. Not only is it oxidized, but the cleavage products, ecgonine, benzoic acid, etc., are oxidized.

8. Local and anesthetic action of cocaine.—Cocaine owes its present therapeutic position primarily to the fact which was first emphasized by Koller in 1884. This action is dependent upon the fact that when cocaine is brought in contact with the tissues in sufficient concentration it leads to a temporary narcosis of all nerve

structures, especially of sensory nerve endings. This analgesic effect comes on after five or ten minutes, lasts for a variable time, according to the rapidity with which absorption takes place from the local area, and gradually and completely disappears.

Cocaine is, therefore, admirably adapted to local and minor operations. When injected into the tissues by hypodermic syringe or applied locally as in the case of mucous membranes, the eye, etc., it produces a local anemia from its stimulation of the small blood-vessel walls, also a local analgesia. Solutions of from 0.5 (or weaker) to 2 per cent. are used for this purpose. In every case rapidity of absorption is hindered as far as possible and care must be taken never to allow a maximum dose of more than 50 mg. to be absorbed into the general circulation. Susceptibility varies extremely with different individuals, many are more tolerant, but one grain (66 mg.) is often a toxic dose. With deep analgesia not only are the local sensory endings narcotized but nerve trunks can be cut without pain. For larger nerve trunks it is necessary, however, to inject the cocaine directly into the nerve sheath.

Cocaine is also used for major operations by the method of spinal analgesia. For this purpose cocaine is injected directly into the meninges around the spinal cord, the puncture being made between the laminae of the lumbar vertebrae. As the drug diffuses around the meninges of the spinal cord it produces a temporary spinal paralysis and this persists long enough for elaborate and extensive surgical operations. The first major operation of this type was executed by Bier in 1898, the operation being the resection of a tubercular foot under spinal analgesia produced by 3 cubic centimeters of a 0.5 per cent. solution of cocaine.¹ The limit of the spinal use of cocaine is set by the presence of the nerves of vital function having their origin from the cervical cord. Of course spinal analgesia cannot safely be carried to the cervical region, since the loss of function of the phrenic nerves, arising from the third and fourth spinal nerves, will lead to respiratory paralysis.

9. The cocaine habit.—The use of cocaine, like alcohol, morphine, etc., leads to the formation of the habit. Under the cocaine habit the individual has an irresistible craving for the drug. The body becomes more and more tolerant, therefore correspondingly stronger doses are required to produce the desired stimulations.

¹ Murphy, John B.: "Analgesia from Spinal Subarachnoid Cocainization," *Jour. of Am. Med. Association*, Vol. XXXVI., p. 359, 1901.

Cocaine is very much abused, especially in America, where it is said to have reached a widespread use among the negro population, as well as among the whites.

IV.

Substances Which Produce Anesthesia Similar to Cocaine.

The cocaine nucleus permits chemically of a number of substitution products, and a knowledge of the factor which contributes to the anesthetic properties has led to the development of a long series of compounds of this group.

In the development of these compounds the attempt has been made to produce drugs which increased the anesthetic effects and as far as possible diminish the undesirable and toxic effects of cocaine. Of these synthetic and substitution products the most important, together with their variations from the cocaine reaction, are as follows:

Tropacocaine. This synthetic alkaloid produces effects very similar to cocaine. The main differences are that it acts more rapidly, produces little or no dilation of the pupil and less vasoconstriction. Its anesthetic power is slightly greater than cocaine, and it is somewhat less poisonous.

Eucaïne. Two synthetic eucaines with an eegonine foundation have been produced. α Eucaïne ($C_{19}H_{27}NO_4$) was the first produced and used, but it has been abandoned because of its marked irritant action. β Eucaïne ($C_{15}H_{21}NO_2$) enjoys a certain amount of popularity because of its lessened toxicity, one-fifth as toxic as cocaine. It produces neither vasoconstriction nor mydriasis. It is slightly less stimulating to the central nervous system and has a less tendency to produce convulsions than does cocaine. It does not decompose on prolonged boiling as does cocaine.

Stovaine produces a similar local anesthesia to cocaine. It has the advantage in that it is more soluble and less toxic.

For hypodermic and intramuscular injections it has the very great advantage in that it can be sterilized without decomposition. It leads to vasodilation rather than to the constrictor spasms which characterize cocaine.

Holocaine is a coal tar product, produced by the interaction of phenacetine and paraphenetidine. It is more poisonous than cocaine, produces quicker anesthesia without vasoconstriction, has some anti-

septic action, and the effect passes away in a shorter time than with cocaine.

Novocaine is p-aminobenzoylethylaminoethane hydrochloride, with the formula $\text{CH}_2(\text{C}_6\text{H}_4\text{NH}_2\text{COO})\text{CH}_2[\text{N}(\text{C}_2\text{H}_5)_2]\text{HCl}$. Chiefly through its extensive use by Crile and by Bloodgood as a reliable local anesthetic to be depended upon in major surgical work, this drug has come into prominence in the last two or three years. It is said to be less toxic than other cocaine substitutes, and is a "prompt and powerful anesthetic." Novocaine is not strongly irritant. In practice it is often combined with some vasoconstricting drug like epinephrine.

Other substances produce a degree of sensory anesthesia, as for example the coal tar phenol, creosol, etc.; aconite, veratrine, etc.; and the alkaloid yohimbine.

V.

Condensed Summary of Action.

Cocaine is an alkaloid which has an initial general stimulating effect followed by narcosis and final paralysis as toxicity proceeds. Its peculiar interest is associated with its ability to produce local and temporary anesthesia which comes on about five minutes after application, and disappears in fifteen to thirty minutes with recovery of function. In local application it is peculiarly selective of sensory mechanisms but acts on all tissues. In spinal analgesia there is a local narcosis of the spinal cord and nerves originating therefrom, leading to loss of pain in that portion of the body the innervation of which passes through the local segment of the cord. In therapeutic quantity the central nervous system is at first stimulated, the effect passing over into depression and narcosis to a degree depending upon the concentration of the cocaine. The nerve structures readily recover from cocaine provided vital functions are maintained until the alkaloid is sufficiently oxidized or eliminated. Hence its toxicity is in large degree due to a true narcosis. The vital centers of the medulla are sharply stimulated by the therapeutic dose; respiration being accelerated, the tone of the vagus center increased, and the vasomotor center stimulated. The spinal cord is less vigorously influenced, but reflexes are at first accelerated, then depressed, the action being more acute on the sensory connections in the cord. The circulatory system is strongly stimulated. There is peripheral vasoconstriction chiefly from stimulation of the vasomotor center, but

partially by local nerve-end stimulation. In local anesthesia the blood-vessels are characteristically contracted, leading to a blanching of mucous membranes, etc. The heart is influenced in opposite directions by the simultaneous stimulation of the inhibitory nervous mechanism and of the cardiac muscle. The nerve influence is more acute and briefer, hence is dominant in the earlier stage, while the muscular influence is dominant in the later stage. The amount of muscular work is increased, primarily through the action of cocaine on the voluntary motor nerves, but secondarily through a direct favorable influence on the striated muscle. However, consecutive tests on soldiers and athletes indicate that the drug is of little or no permanent value.

Locally applied to the eye, cocaine produces dilation of the pupil and partial loss of accommodation. The light reflex persists, hence the iris reflex mechanism is not affected. The dilation is due to stimulation of the nerve endings of the radial muscles. Cocaine is fully oxidized in the body, but sometimes a little is excreted through the kidney. There is a tendency to habit formation with a great increase in tolerance in the body.

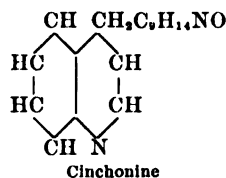
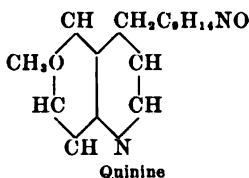
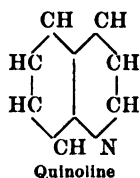
CHAPTER XXVIII.

QUININE.

I.

Historical and Chemical.

The bark of different species of the Cinchona tree, *Cinchona succirubra*, etc., yields a series of over twenty alkaloids of varying composition. Of these the quinine, quinidine, cinchonine, and cinchonadine are of special importance. These alkaloids are quinoline derivatives as illustrated by the following formulæ:



II.

Outline of Pharmacological Action.

Quinine produces its results in the body because of its toxicity to protoplasm of all kinds, the action being strongest on undifferentiated protoplasm. It produces a very mild initial stimulative increase in function, followed by marked depression and loss of function, hence:

1. *Toxicity to protoplasm of all kinds.*
2. *Specific, i.e., selective toxicity to undifferentiated protoplasm such as white blood corpuscles, malarial plasmodia, etc.*
3. *Antipyretic action by the primary decrease of heat production with secondary increase of heat loss.*

III.

Details of Pharmacological Action.

1. **Systemic action.**—The pharmacological effects of quinine are directly traceable to its great toxicity for all kinds of protoplasm. In

this regard it differs, however, from members of the aconite group in that the irritant and antecedent effects are very much lower and its depressing effects before the final intoxication occurs more profound. The general symptoms in the mammalian body are those dependent upon the general toxic activity throughout the organism. They will be better understood upon examining the behavior of different tissues after subjection to quinine.

2. **Action on undifferentiated protoplasm.**—The greater intensity of action of quinine on undifferentiated protoplasm accounts for its most important use, i.e., to destroy the malarial parasites when they infect the body. This therapeutic quality was discovered empirically early in the seventeenth century, long before the scientific reason was understood, either as regards the active alkaloid or the identity of the invading parasite.

Binz¹ in 1867 determined that quinine was poisonous to certain one-celled animal forms, also to the white blood corpuscles. Vorticellæ became inactive in 0.2 per cent. solution and actinophrys in 0.1 per cent. withdrew its pseudopodia, its protoplasm became more granular and darker. He showed that fresh water amebæ are very sensitive to quinine, though, strange to say, the salt water forms are much more resistant. White blood cells kept at a temperature of 35°C. in a moist chamber are actively motile. When mounted in serum containing 0.05 per cent. quinine this motility fails to develop and the white corpuscles remain round and darkly granular.

Parasitic ameboid forms, such as the dysentery ameba and the malarial parasites, are also particularly susceptible to the influence of quinine. Quite recently its use has been advocated in rabies on the view that the Negri bodies are ameboid in nature. The malarial parasite runs a cycle of change in the body. It develops in the red blood corpuscles to a certain stage, then passes out into the blood plasma in an active free swimming form. This critical period in the life cycle of the malarial parasite is the one at which toxic substances are liberated into the body, and at this time the characteristic malarial symptom of paroxysms followed by fever occur. The motile malarial organism is peculiarly susceptible to quinine, hence, if it is present in the blood plasma in sufficient strength at this time the germs will be destroyed and their regeneration in a new cycle prevented.

An influence in the body depending upon this general toxicity is felt on the white blood corpuscles, as can be demonstrated on the frog

¹ Binz, C.: *Archiv f. Mikroskopische Anatomie*, Vol. III., p. 383, 1897.

or the mammalian leucocytes. A prolonged and profound application of quinine may lead, therefore, to a reduction of the number of leucocytes, a fact which secondarily influences other conditions in the mammalian body.

3. Quinine as an antipyretic.—The normal and constant temperature of warm-blooded animals depends upon regulating the heat through the interaction of two complex sets of factors: (1) the factors that contribute to the regulation of heat production, and (2) the factors interacting for the regulation of heat loss or heat dissipation.

The production of the heat of the body is a direct result of the oxidations taking place during the metabolism of the tissues. Any and all factors which vary the intensity and amount of tissue oxidative changes will, of necessity, cause a variation in the amount of heat produced. The most active tissues of the body are the muscles and glands, both of which are under nervous regulation and coördination. But of all the heat producing tissues the greatest in mass and the greatest in intensity of oxidative process are the voluntary muscles. These are, therefore, the chief source of the body heat. Heat production takes place through oxidative changes in the skeletal muscles more or less independent of the liberation of active motion during the phenomenon of contraction (Pflüger's chemical tonus). The glands also produce considerable quantities of heat in proportion to their mass metabolism. Both these sets of organs vary in their oxidative activity under the influence of an elaborate nervous mechanism over which certain centers in the brain-stem have primary regulative influence. The chief center or centers that concern us in this relation are the thermogenic centers of the corpus striatum, the heat centers. Subsidiary centers are present in the mid-brain and the medulla, but the spinal animal does not possess regulative control of heat production. Heat production, therefore, may be varied by varying the activity of the thermogenic center. This center, like other nervous regulative mechanisms, is acting in response to the inflow of sensory stimulation and gives rise to nerve impulses in proportion to the sum of the algebraic factors, (1) volume of inflowing stimulation, and (2) the relative irritability of the center itself. As a matter of fact there are three instead of two links in the regulative chain controlling heat production. Beside the two just given there is, (3) the condition which varies the ability of the terminal motor tissues to respond to a given nerve stimulus. There is a rise or fall of motor tissue stability under the

influence of normal variations in the nutritive condition, or of pathological factors in the environment, both very prone to react through this third factor.

Heat loss or heat dissipation is measured by the output of heat from the surface of the body through the three physical processes, *a*, heat radiation; *b*, heat convection, and *c*, heat loss through evaporation of moisture. Heat radiation and heat convection occur in proportion to the relative temperature of the surface of the body and its immediate environment. Loss of heat through evaporation of moisture bears a similar relation to environment, but is primarily dependent upon the amount of moisture thrown on the surface by the sweat glands. The surface temperature of the skin during the times when heat is being rapidly lost from that region bears a close relation to the volume of blood flowing through the skin per unit of time. Whenever the cutaneous blood-vessels are markedly dilated and there is an increase in the circulation of blood through the skin, there is a rise in surface temperature and heat loss through conduction and radiation is greatly increased, unless perchance the external temperature is actually greater than that of the skin. Incidentally, the better cutaneous circulation is also favorable to increased activity of the sweat glands.

Heat loss, therefore, is also regulated, i.e., coördinated by nervous mechanisms, in this case primarily two mechanisms, (1) the sweat secretory apparatus, and (2) the nervous factors which control the circulation, both general and local. When the sweat glands are stimulated by the secretory nerves there is a corresponding increase in the formation of sweat with its accompanying increased evaporation from the surface and resultant greater loss of heat. This stimulation of the sweat-producing apparatus is almost invariably associated with a corresponding stimulation of the vasodilator mechanism from the skin.

It will be seen, therefore, that the constant temperature of the body involves the coördination of several nervous mechanisms, one group, the regulators of heat production, the other, the regulators of heat dissipation. These factors are maintained in balance at various levels in the different species of animals.

Normal Temperature.

Man	37°C.
Dog	38°C.
Rabbit	38.6°C.
Guinea-pig	37.6°C.
Chicken	41°C.

These heat levels in the given species are remarkably constant under the widely varying conditions of external temperature. Yet a slight disturbance of the relative irritability of any one of the various coördinative nerve centers may decidedly change the average temperature level at any time. This is illustrated by the results of puncture of the corpus striatum, also by fever resulting from the toxins of bacterial infection, or by other pathological conditions.

Following brain puncture there is a gradual rise of level of heat equilibrium in an animal of from 1 to 3 degrees. Numerous studies of brain puncture,¹ have shown that there is an increase of heat production during the rise of temperature, rather than a decrease of heat loss. In other words, the puncture serves as a mechanical stimulus of the thermogenic center and this leads to a rise of heat production without a corresponding increase of heat dissipation sufficient to maintain the temperature of the body at the normal level. The result is that the temperature is raised.

Two Experiments showing the effects of Heat Puncture in the Rabbit on heat production, heat loss and body temperature (from Schultze).

Animal.	Stage.	Temperature Centigrade.	Heat loss per hour.		Heat produced per hour.	
			Calories.	Per cent. of normal.	Calories.	Per cent. of normal.
1	Normal	38.5-38.6	6.46	100	6.49	100
	During rise	38.6-39.6	6.87	106	7.67	118
	Climax	39.6-39.5	7.71	120	7.64	118
2	Normal	38.7-38.9	7.22	100	7.28	100
	During rise	38.2-41.0	7.97	110	9.63	132
	Climax	41.0-41.2	8.70	120	8.88	122
	Second day	40.8-40.8	8.40	123	8.42	121

At this new level, heat regulation can still be maintained. In other words, a shift in the point of heat equilibrium does not necessarily destroy the reflex responsiveness of either the thermogenic centers or of the blood vascular and sweat centers, the reactions of which control heat loss.

In fevers, likewise, the disturbance of the balance between heat loss and heat production leads to a rise of temperature of the body but without loss of the temperature reflexes. In other words, there is a degree of heat regulation still shown under the fever condition, though the ability to maintain the temperature at the normal level

¹ Schultze, Otto: *Archiv f. Path. u. Pharm.*, Vol. XLIII., p. 193, 1900.

is lost. Here, again, certain fevers depend upon a rise of heat production and the picture can readily be explained as a heightened irritability of the thermogenic center.

Light is thrown upon the situation by considering what occurs under normal conditions during excessive physical activity. An enormous increase in heat production takes place with a rise of the temperature of the blood of the body. The increased temperature of the blood reacts through stimulation of the peripheral sensory mechanisms, i.e., sense organs of heat, leading to reflexes that react through the centers concerned in both heat production and heat dissipation. The warmer blood flowing through these brain centers also acts directly on the nerve cells, especially those of the great medullary centers. The rise of blood-pressure within physiological limits also reacts on the nerve centers, contributing to an increase in their irritability. In the normal animal, under these conditions, the increase in irritability of the sweat and vascular centers is great enough to increase heat dissipation to a point that will quickly bring the temperature down to the normal, and in prolonged activity hold it there. In an animal in fever, in the case of puncture fever particularly, the stimulus falls directly on the thermogenic center. The mechanical stimulus of the puncture keeps this center in a state of hyperirritability which cannot be entirely overcome by the action of the heat dissipating centers. In fever from toxemia the phenomena are so similar that one may believe that there is a degree of toxic action (possibly selective) on the thermogenic center which increases its activity in a way comparable to the puncture fever.

When quinine is given it leads to a fall of temperature, a change that is most pronounced if the body is already in the condition of fever. This fall of temperature takes place before there is a corresponding increase in loss of heat, a complex that has been investigated by Gottlieb. This observation shows that the lowering of the temperature is in reality a primary lowering of heat production. Now quinine does not interfere with the output of carbon dioxide in normal animals, but it does result in a marked diminution in the excretable nitrogen. Tissue metabolism is therefore reduced, and since this reduction takes place when the brain and medulla are separated from the cord (Binz), it is evident that the primary influence of quinine is directly on the tissues in which the heat is evolved rather than in the lowering of the irritability of the thermogenic center itself or on the sensory side of this reflex arc. In fact the center is still reflexly responsive. However, in explanation of the

favorable action of quinine in fevers dependent upon hyperirritability of the thermogenic center one can scarcely exclude a degree of narcotic action on this group of nerve cells.

Gottlieb's experiments¹ show that the lowering of temperature will take place independent of change in heat dissipation. However, he observed that under certain conditions there was an actual lowering of the heat output. Quinine often produces a vasodilation in the blood-vessels of the skin and a corresponding increase in heat loss, a result that is readily explained by consideration of the toxic influence on the blood vascular system. If the toxicity leads to that degree of vascular paralysis in which the cutaneous vasomotor tone is lost, then this factor of heat dissipation assumes a more important rôle.

The antipyretic action of quinine, therefore, is twofold: (1), chiefly a toxic lowering of tissue metabolism and therefore heat production, accompanied by a certain but slight degree of diminution of irritability of the thermogenic center; and (2), a secondary cutaneous dilation, especially in the rather toxic stage, with corresponding increase of heat loss. The absolute loss of course diminishes in the later stages of the reaction. The greatest antipyretic action of quinine is noted under pathological conditions or in brain puncture where the fever is due to hyperirritability of the tissues. But in normal animals there is also a lowering of temperature by quinine, showing that its peculiar influence is not limited to the special pathological case, but is general.

4. **Action of quinine on muscle.**—Quinine is very toxic to skeletal muscle, producing a marked decrease in the power to do work. Even solutions of 1 in 50,000 are depressant to this tissue. The onset of the depressant action in the toxic concentrations is introduced by a brief and transient period of heightened irritability. The depressing action is proven to be directly on the muscle substance since it occurs when the nerve endings have been eliminated.

Certain organs, such as the spleen, undergo a degree of contraction under the influence of quinine, which suggests that smooth muscle tissue has a somewhat greater initial stimulative reaction to quinine than most parts of the body. Larger doses produce depression of function.

5. **On the digestive tract and on digestion.**—Quinine possesses a very bitter taste, hence reacts locally on the reflex mechanism of the mouth. The bitter taste leads to a strong reflex which gives

¹ Gottlieb, R: Schmiedeberg's *Archiv*, Vol. XXVI., p. 419, 1890. Also Vol. XVIII., p. 167, 1891.

quinine the indirect influence of a tonic. The character of the reaction of this class of drug is discussed more fully under the subject of bitter tonics. Larger quantities of the more soluble hydrochloride occasionally produce some local effects on the stomach leading to nausea, in some cases diarrhea.

The digestive processes are lowered by a mixture of the enzymes with the quinine, presumably by direct destruction of the enzyme itself.

6. **On the liver.**—Quinine leads to a depression of the glycogenic function of the liver. This reaction is explained as a result of the toxic lowering of the amount of glycogenic ferment due to the depression of function of the liver parenchyma.

7. **On the central nervous system.**—Beside the effect on the heat regulative center the general nerve structures undergo a depression of function ending in paralysis. This is demonstrated through the influence of the drug on the sensitiveness of the responses of the cerebral cortex. There is often noted after relatively large quantities of quinine a distinct interference with the special sense organs, especially of the ear and eye, partial deafness being a peculiarly characteristic after result of the continued display of the drug.

8. **The elimination of quinine.**—The alkaloid quinine is relatively insoluble and its absorption takes place only slowly from the alimentary tract. The hydrochloride is rather more readily absorbed because of its greater solubility. In the body a large quantity, 70 to 75 per cent., is oxidized and disappears. The remainder is excreted unchanged by the kidney. Only traces of quinine are excreted in the feces. Schmitz¹ has carefully investigated this question. His results show that of the quinine administered by the mouth about one-fourth to one-third is slowly regained from the urine. The following figures, quoted from him, illustrate this point.

Experiment I.,	0.817 gr. quinine given,	.217 gr. recovered	= 26.6 per cent.
" II.,	0.817 gr. " "	.244 gr. " "	= 29.9 "
" III.,	1.226 gr. " "	.346 gr. " "	= 29.7 "

When the quinine was introduced subcutaneously it was excreted more slowly, as shown in the following table, also from Schmitz:

¹ Schmitz, Richard: Schmiedeberg's *Archiv*, Vol. LVI., p. 301, 1907.

DAY.	Quinine given daily.	24 hour urine in cc.	Quinine recovered.	Per cent.
Second.....	0.605	1400	0.108	17.9
Third.....		1700	0.120	19.8
Fourth.....		1400	0.083	13.7
Fifth.....		1450	0.128	21.1
Sixth.....		1600	0.076	12.6
Seventh.....		1500	0.071	11.7

This shows an average daily recovery of 16.1 per cent. of the amount of quinine given.

The human body does not acquire any marked tolerance, as shown by the usual method of determination by the increased power of oxidation. This Schmitz determined on an individual who excreted an average of 25.3 per cent. of the quinine given during the first seven days, while five weeks later he excreted 26.9 per cent.

IV.

Condensed Summary of Action.

Quinine and its closely related alkaloids are protoplasmic poisons which show a minimum initial stimulation and a prolonged paralytic after effect. Undifferentiated tissues, such as the white blood corpuscles, the general type of tissue cells, as connective tissue, etc., and micro-organisms, such as amebæ and the malarial parasites, present the greatest susceptibility, approaching that of specific reaction.

As might be expected, quinine is an antipyretic of value. There is a decrease in body temperature in the normal body, but a more conspicuous decrease occurs in fevers. The reduction is primarily through depression of the function of the thermogenic tissues. The muscular tissues show an initial slight stimulation chiefly in contractility, followed by a marked depression of ability to do muscular work. This effect is true for skeletal muscle, cardiac muscle, and smooth muscle. The nervous system is depressed by the lowering of the irritability of the nerve cells of whatever type. The effect shows itself through interference with the action of the cortex in interpreting visual and auditory sensations and with other coördinative centers of the central nervous axis. There is a slight bitter tonic effect on the digestive tract, but this is more than counterbalanced by the lowering of the efficiency of the digestive enzymes. Quinine is very readily absorbed from the alimentary tract, is slowly oxidized by the tissues and excreted unchanged to the extent of 25 to 30 per cent. by the kidney.

H. *The Coal Tar Series*

CHAPTER XXIX.

THE COAL TAR ANTIPYRETICS.

I.

Historical and Chemical.

The chemical separation of the coal and wood tar products has yielded a long series of carbon compounds, many of which have important influences on the functions of the body. The most important of these compounds pharmacologically are those that have as their base the benzene nucleus, often, it is true, fundamentally modified.

The distillation of many woods and wood tars also, especially of the pines, beeches, etc., yields compounds of this series, of which the creosotes are an illustration.

The coal tar products are characterized by their toxic influence on living protoplasm, a toxicity that varies widely with the exact compound. But for convenience in presenting their pharmacological actions the numerous members of the series will be treated in two sub-groups: the Antipyretics and the Antiseptics.

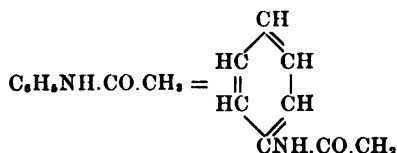
The older antipyretics are such drugs as aconite and quinine. These, in recent times, have been very largely superseded by the antipyretics of the coal tar series. The introduction of phenol as an antiseptic by Lister¹ in 1867, which so profoundly revolutionized our surgical technique, was soon followed by the important discovery that its carboxyl derivative, salicylic acid, produced a marked fall of body temperature. This antipyretic action of salicylic acid was soon extended to phenol itself and to others of the simpler phenol series.

The almost limitless possibility of variation in structure of both nucleus and side chain among the ring compounds has led to the isolation, and, in many cases, synthetic production of numerous compounds, which are theoretically possible, according to the laws of chemical substitution.

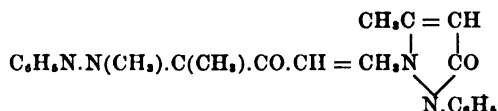
¹ Lister, Sir Joseph: *British Medical Journal*, Sept. 21, 1867.

Phenol is sharply toxic to protoplasm and its antipyretic action is secured with danger. The attempt has been to reduce toxicity and if possible retain or strengthen the antipyretic action. Many of these preparations have been manufactured and thrown on the market, often under trade names, and without adequate therapeutic testing. Of the series that have proven of distinctive antipyretic value and which have now been used and tested through a number of years until their pharmacological actions are well proven may be mentioned:

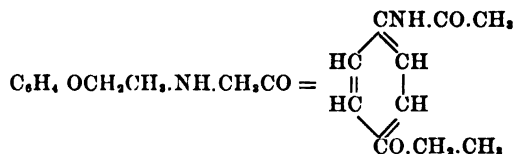
(1) Acetanilide, an aniline derivative with the formula:



(2) Antipyrene, which is a phenyl-dimethyl-isopyrazolon, with the formula:



(3) Acetphenetidine (phenacetine), with the formula:



To this series one might add members of the group of salicylates, which have considerable antipyretic action. Especially to be mentioned are ethyl salicylate (oil of wintergreen) and acetyl salicylic acid (aspirin).

II.

Outline of Pharmacological Action of the Coal Tar
Antipyretics.

The chief activity of the subgroup is expressed by the name, and is therefore:

1. *Antipyretic.*
2. *A tendency to reduce oxy-hemoglobin to methemoglobin.*
3. *General toxicity.*
4. *Analgesic action.*
5. *Initial slight stimulation, followed by prolonged depression and paralysis of differentiated tissues, intensity of action greatest for nervous tissue.*

III.

Details of Pharmacological Action.

1. The general antipyretic action.—Under the chapter on quinine a review of the normal mechanism for the regulation of heat in the body for those animals that have a constant temperature is given. Attention is called there to the two regulative factors, heat production and heat dissipation, both of which are under nervous control. It is there explained that heat production which takes place in the tissues is regulated through definite nervous centers in the brain-stem. Heat loss, on the other hand, is a factor of heat dissipation from the surface of the body. So far as the body is concerned, the rate of loss of heat and its regulation will depend chiefly on variations in the two factors, i.e., the circulation through the skin and the activity of the sweat glands.

The coal tar antipyretics depress the vasomotor tone, hence lead to marked vasodilation, particularly in the skin. This physiological change produces an immediate increase in the relative warmth of the skin, a factor which is favorable to the loss of heat. The change in the circulation in the skin favors an increase in sweat production, adding still a third factor favorable to heat loss. In the therapeutic intensity of action the thermogenic center is still responsive to stimuli, hence at this stage there will be an associated actual increase in heat production. Under the more pronounced influence of the coal tar antipyretics the activity of the thermogenic center itself is depressed, hence there is a decrease in heat production. These factors

were determined on rabbits by Gottlieb.¹ He contrasted the antipyretic action of quinine and the coal tar products, showing that whereas quinine primarily depresses thermogenesis with little or no change in heat loss, antipyrine greatly increases the heat dissipation, which is the primary source of its ability to depress the body temperature. In the more intense action it also decreases heat production, a factor that is relatively secondary in this group.

2. **Narcotic action of the antipyretics on the central nervous system.**—The antipyretics as one characteristic of their action produce a decrease in the sensitiveness of the nerve centers to reflex stimulation, therefore are analgesic. This narcotic factor has led to their use (and abuse) in cases of severe migraine. Acetanilide, which is the most widely used in this connection, is decidedly, in fact dangerously, toxic. Even with mild dosage there is some depression of reflex irritability, indicated by a greater drowsiness and sluggishness than normal. In toxic quantity acetanilide produces cyanosis and convulsions in both man and mammals. These latter effects have been ascribed to lack of coördination of the nerve reactions through the spinal cord to a degree approximating to strychnine poisoning. The convulsions are to some extent, but by no means wholly, traceable to the cyanosis and asphyxiation, which occur at the same time.

3. **On the circulation.**—The effects of the coal tar antipyretics on the circulatory system are threefold: First, cardiac; second, vasomotor; third, on the blood.

Studies on the frog's heart show that the initial rhythm is accelerated, but that this is followed by decided cardiac slowing. The cause of the behavior of the heart is best shown by studies on isolated heart muscle. The toxic action can readily be shown on isolated strips of terrapin heart. This line of experimentation shows that it takes careful gradation of dosage to develop the stimulating action of the antipyretics, for example, acetanilide. Solutions of from 0.02 to 0.04 per cent. of acetanilide in weak Ringer's solution or in physiological saline lead to acceleration in the rhythm of heart strips, occasionally accompanied by increased amplitude. But a very slightly stronger solution, while it may produce one or two beats with accelerated rhythm, invariably leads to slowing and sometimes complete cessation of the rhythm.

Toxic solutions (up to saturation, i.e., 0.5 per cent.) produce a slow and weak rhythm followed by a pause. The initial contractions may be more or less incoördinated and show a tendency to fibrillation.

¹ Gottlieb, R.: *Archiv f. Exper. Path. u. Pharm.*, Vol. XXVI., p. 419, 1890.

Even these solutions are not immediately toxic, since after strips are returned to normal solutions they finally recover fully. It is evident, therefore, that acetanilide produces its effect in the frog's heart too by a narcotic depression of cardiac muscle.

The blood-vessels are dilated under the antipyretics, a condition which may be preceded by a slight but insignificant vascular constriction, with associated higher blood-pressure. Certainly in the toxic stage the blood-pressure is low, the blood stream stagnated with pronounced cyanosis. These effects are due to the general paralysis of the vasomotor nervous mechanism, leading to a reduction in the resistance to peripheral blood flow. However, the cardiac depression will also account for some percentage of the decrease in blood-pressure.

The blood is affected through the formation of methemoglobin, especially marked with acetanilide, though with antipyrine the action does not take place to so profound a degree. As the dose is increased and the toxic action comes on the disintegrating red blood cells set methemoglobin free in the blood stream. It is finally excreted by the kidney and makes its appearance in the urine. The methemoglobin action is produced largely by the decomposition product, para-amidophenol, which occurs on oxidation of acetanilide in the body. The fact that antipyrine is not so readily oxidized and does not so rapidly give rise to this compound explains its failure to produce oxy-hemoglobin. Of the three representatives of the series chosen, acetanilide is the most toxic to the blood and phenacetine the least.

4. **Variations in susceptibility.**—There is unusual variation in individual susceptibility to the members of the coal tar antipyretic series. The general literature notes numerous cases of recovery after enormous doses, and at the same time of deaths that have occurred from relatively small doses. Children are particularly susceptible, and a greater reduction in dosage allowance for them than is called for by the rule must be made. In children the tissues are in an active stage of growth. Their protoplasm is relatively undifferentiated, and, as is true for most substances toxic for general protoplasm, their tissues are particularly susceptible to chemicals of this series.

The narcotic action of the coal tar antipyretics has led to their extensive use in the so-called headache remedies, a use fostered to an undesirable degree by chemical manufacturers and of course by the medical charlatans. The methods contributing to the extensive use of these drugs as home remedies are responsible for a large percentage of the fatalities that have occurred therefrom. The toxicity of the

series is entirely too great to justify use except under the direction of a physician. The abuse of this principle has resulted in numerous cases of collapse and an occasional death that might otherwise have been prevented.

5. Comparison of acetanilide, antipyrine, and acetphenetidine.—Of the three drugs the least toxic, possibly because it is least soluble,

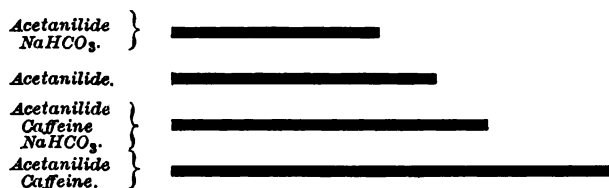


FIG. 62.—The relative toxicity of acetanilide in combination with sodium bicarbonate and caffeine. From Worth Hale.

is acetphenetidine; the most toxic, antipyrine. Acetanilide particularly is oxidized in the body to para-amido-phenol, to which form its general effects are often ascribed. The phenol acts on the red blood corpuscles, producing methemoglobin. The antipyrine also produces methemoglobin. It is oxidized to the para-amido-phenol more slowly, hence the substance can be taken care of by the body without so intense a reaction with the hemoglobin. Worth Hale has demonstrated that caffeine added to acetanilide greatly increases its toxicity. Sodium bicarbonate tends to reduce the toxicity of acetanilide, also the toxic action of acetanilide and caffeine.

CHAPTER XXX.

THE COAL TAR ANTISEPTICS.

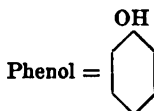
I.

Historical and Chemical.

The coal tars yield a long series of antiseptics, i.e., drugs which are particularly toxic to generalized protoplasm, and therefore to bacteria and other lower organisms.

An ideal antiseptic for the human body is one that is toxic to any foreign invading organism, bacterial or otherwise, and at the same time non-toxic for the tissues of the body itself. It is expecting too much to suppose that we can with our present state of chemical knowledge attain this ideal, but the goal is worth striving for, and the works of such men as Ehrlich give promise that we may reach it at a day not so very far distant in the future. That the protoplasm of bacterial organisms is similar to that of the human organism in its fundamental composition cannot be denied. That there is a differentiated structure for bacterial protoplasm also goes without saying. The point to be desired in the antiseptic is that it may so chemically combine with some characteristic structure of the organism as to become toxic without at the same time forming disadvantageous combinations with the protoplasm of the tissues of the host. The success of Ehrlich in synthetically developing the organic arsenic compound, arsenobenzol, stands to-day as our best illustration of the modern tendency of research in this field.

Benzene, C_6H_6 , the base or nucleus on which are built numerous series of coal tar preparations, is practically incapable of chemically combining with protoplasm. But this nucleus is chemically wonderfully labile, since it permits of innumerable substitutions for the hydrogen atoms of the ring, and, as we have already seen in the antipyretics, for the carbon as well. The substitution products carry the ability to attach the ring to the chemical substances entering into the composition of protoplasm. As an example, when one hydrogen is substituted by one oxy-hydrogen, phenol is formed.

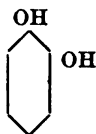


Phenol is wonderfully toxic to protoplasm, therefore antiseptic. The toxic and antiseptic properties of the benzene nucleus increases with the number of attached OH groups in the order illustrated by the following:

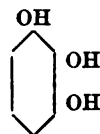
Toxicity increases from Phenol to Pyrogallol



Phenol



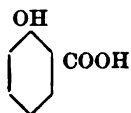
Resorcin



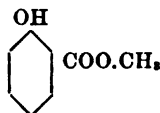
Pyrogallol

The toxicity is due to two factors, (1) the greater combining ability, and (2) the property of the hydroxyl grouping.

The toxic and antiseptic action of the phenol compounds is changed somewhat with the introduction of other nuclei in the side chain, as, for example, in salicylic acid or in methyl salicylate.



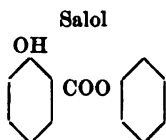
Salicylic acid



Oil of wintergreen

Salicylic acid is much less toxic to the human body than phenol. This property makes it less irritant to mucous surfaces. Its somewhat lesser degree of solubility in the tissue fluids also reduces its toxicity. The introduction of other radicles, such as methyl, CH_3 , etc., adds the pharmacological action of the new group, which may cause variation either in the stimulative phase or in the toxic phase of the action of the original product.

The antiseptics of the coal tar series also owe their toxicity in some degree to the decomposition products, as is illustrated very well by the explanation of the methemoglobin formation in the case of acetanilide. In the body these decompositions may set free active antiseptic compounds, as illustrated by salol.

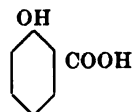


Salol

Decomposition products



Phenol

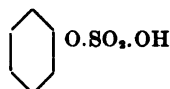


Salicylic acid

In like manner the body protects itself by the formation of inert compounds. The phenols and phenol derivatives are largely oxidized to phenol sulphate and other relatively inactive compounds, in which form they are rapidly excreted by the kidney.



Phenol



Phenol sulphuric acid

It would be out of place to treat specifically every member of this enormous group of compounds. For our purpose it will be better to illustrate the group by specific treatment of the most important types. For this purpose we will take (1) the phenols, (2) the salicylates, and (3) the creosotes.

II.

Outline of Pharmacological Action of the Coal Tar Antiseptics.

1. *General toxicity for all kinds of living protoplasm.*
2. *This toxicity manifests itself in an initial but slight stimulation phase, followed by a narcosis and paralysis.*
3. *Peculiarly toxic to the nerve centers of the central nervous system.*
4. *A certain degree of anesthesia to local sensory mechanisms.*
5. *Toxic to the blood with the formation of methemoglobin.*

I.

THE PHENOLS.

Phenol, or carbolic acid, is the oldest and best known of the coal tar antiseptics. It is derived from benzol by the substitution of one hydroxyl, thus, C_6H_5OH . It was phenol which Lister first introduced into antiseptic surgery in 1867.¹

III.

Details of Pharmacological Action.

1. **Toxicity to protoplasm.**—Phenol owes its antiseptic quality to its solubility in, and toxic chemical avidity for, protoplasm. It

¹ Lister, Sir Joseph: "On the Antiseptic Principle of the Practice of Surgery," *British Medical Journal*, Sept. 21, 1867.

acts somewhat more strongly on undifferentiated protoplasm, such as bacteria, protozoa, etc., but it is relatively toxic for all kinds of differentiated tissue. As an antiseptic to be used in surgical sterilization and dressings, it is customary to use solutions of from 3 to 5 per cent. The latter solution is not only germicidal, but quite toxic for exposed tissues, hence when kept in long contact leads to degeneration and disintegration.

More dilute solutions of phenol will destroy active bacteria if kept in contact for a sufficient length of time, in the course of a few minutes with certain forms, while others resist for hours or even days. Bacterial spores are the most resistant forms of living matter to the action of chemical poisons. The spores of anthrax are particularly resistant in this regard. They withstand the toxic action of the stronger solutions of phenol for many hours.

The typical action of phenol on general protoplasm is the production of a degree of local irritation. This is especially the type of action when phenol is applied to mucous membranes. When carbolic acid is swallowed the local corrosive action on the mouth and stomach leads to irritation accompanied by the reflexes expressed in nausea and vomiting. This is particularly true of gastric irritation from this source. Such reflexes may and often do follow non-toxic amounts of the drug. Phenol is easily soluble and readily absorbed, therefore, in addition to the local reflexes from gastric irritation, the substance quickly produces its systemic effects, especially when there is a possibility of being absorbed through abraded surfaces.

2. On the central nervous system.—Carbolic acid produces a slight and transient stimulation of the cells of the central nervous system, but the main picture is one of toxic depression and collapse. The collapse appears early and after a relatively slight amount of absorption. It is due to the action of phenol on the basic nuclei of the brain-stem and cord. The initial stimulating effect on the great regulative centers is slight, but shows itself through rapid respiration, accelerated pulse, and other vascular disturbances. The stage of toxic collapse quickly follows through a depression of, (1) the irritability of the thermogenic center, which leads to a lowering of heat production, (2) through a paralysis of the vasomotor and cardiac centers of the medulla, deranging the efficiency of the circulation, and (3) by paralysis of the respiratory center leading to shallow respiration, asphyxia, and death. The spinal cord is affected in such a way as to interfere with the coördinative control of voluntary nerve impulses. It is apparently this which leads to the irregular contrac-

tions and muscular twitchings, both in the frog and in the mammal, resulting in response to sensory stimulation. The absorption of phenol is so rapid after the swallowing of toxic quantities that this chain of nervous symptoms follows in rapid succession, a fact only too well known from the numerous cases of suicidal poisoning.

3. **On the circulatory system.**—The toxic action on the medullary centers mentioned above of course includes those centers controlling the circulatory apparatus. In therapeutic limits the first influence on the circulatory centers is slightly stimulative. This limit is quickly passed, and there is a marked depression, which shows itself most strikingly on the vasomotor center. With the decrease of response of this center there is dilation of the peripheral blood-vessels and fall of blood-pressure, all contributing to the well-known condition of collapse. The cardiac muscular tissue is also affected by phenol. Perfusions of the heart, as, for example, in the frog, with very dilute phenol solutions (.005 per cent.) lead to an increase in both amplitude and rate. With stronger solutions of phenol this favorable picture is changed to one of marked depression, showing an evident direct muscular toxicity. The circulatory system, therefore, contributes sharply to the total picture of collapse under the influence of phenol.

4. **The excretion of carbolic acid.**—Small amounts of phenol are adequately taken care of by the body of man and eliminated in more or less oxidized form, the oxidation taking place through the hydroxyl bond. Phenol is oxidized into phenol-sulphuric and glycuronic acids, which leave the body by way of the urinary system.

In the oxidation and excretion of phenol, the toxic drug is brought into intimate contact with the renal cells and may produce there local intensity of action sufficient to produce nephritis. As a result the cells of the renal tubules, both of the capsule and the secreting tubules, may undergo toxic degeneration and necrosis, if excretion is rapid enough to produce a sufficient concentration of the drug about the tissues. This is one of the great dangers from the use of benzol compounds as physiological antiseptics. On the other hand, a certain mild degree of local antiseptism may be produced in the excreting organs because of the interaction of the factors just mentioned.

5. **Toxicology.**—The toxicology of phenol is assuming wide practical importance because of its ever increasing use with suicidal purpose. The extensive use of the antiseptic in the arts and for practical disinfection makes it a substance easy for the layman to obtain. Its terrific corrosive action is enough to deter any one from

so unfortunate a choice of suicidal drugs as phenol, but this factor is, probably because of ignorance of the fact, given little weight by our numerous despondents. One gram or less may be a fatal dose, though two or three times this amount may be safely eliminated by the body if introduced through sufficient time. For example, in the days of the use of the Lister carbolic acid spray in surgical work it often happened that large enough quantities were inhaled by the surgeon to produce distinct depression, though no acute toxic effects. Both the absorption and excretion of phenol are rapid, hence the toxic dose will depend largely upon the concentration as well as on the rapidity of introduction. A quantity toxic when suddenly introduced into the stomach may not be so if taken in a series of smaller doses. The stage of collapse and death may come on in 20 to 30 minutes, while death may be delayed for 12 to 24 hours.

In case of poisoning the remedies should be directed toward quick and decisive removal of the non-absorbed phenol, and be followed by symptomatic treatment. Externally phenol is best removed by washing with alcohol or the stronger alcoholic liquors, which dissolve and thus eliminate the drug. When these solvents are not available, then olive oil, sweet oil, or vaseline may be used, as the oils are phenol solvents. Internally phenol may in some cases be dissolved in weak liquors and at once removed by the stomach pump, or it may be partially neutralized by the use of lime water, permanganates, or sulphates. The sulphates do not react with phenol externally, but are an aid to the body in the formation of phenol sulphates during systemic poisoning. Sollmann has shown that too much reliance should not be placed on the sulphates in the case of acute poisoning, although the sulphates are somewhat counteracting in their systemic effects, because they also stimulate where phenol depresses.

Salol is itself not strongly active, but after it passes out of the stomach and is brought into contact with the alkaline contents of the intestine it is broken down into phenol and a salicylic acid component. The released phenol now becomes actively antiseptic, while the salicylic acid produces its typical antipyretic and antiseptic action.

Resorcin, di-hydroxy-phenol, and *pyrogallol*, tri-hydroxy-phenol, are very much more toxic than phenol, the toxicity increasing with the number of OH ions attached. These compounds are still more highly irritant to the tissues. The latter especially is peculiarly toxic to the blood, breaking down the red blood corpuscles with the formation

of methemoglobin. These chemicals are now primarily of interest because of their toxicology.

IV.

Condensed Summary of the Action of Phenol.

Phenol, or carbolic acid, is an irritant toxic mono-hydroxy-benzol, which is toxic to all living protoplasm. The di-hydroxy resorcinol and tri-hydroxy-pyrogallol produce the same type of changes, though they are more intense in action and more toxic. When applied locally phenol produces a degree of irritation, and, if concentrated, corrosion and death of the tissue, whether this be epidermal or mucous membrane. It is rapidly absorbed into the general circulation. The systemic effects are slight and transient stimulation, followed by rapidly developed depression and paralysis. This effect shows most strongly on the central nervous system, particularly the basic nuclei, in which the paralysis leads to depression of the heat regulative center, as well as of the vasomotor and respiratory centers. The general toxic action on the nervous system quickly leads to unconsciousness and systemic collapse, from which the individual does not recover. The motor tissues, the glands, skeletal muscle, smooth muscle, and heart are all sharply depressed, showing a lowering of general metabolism and of specific functional activity. The heart itself is at first accelerated, then weakened and paralyzed by direct action on the cardiac muscle.

Phenol is rapidly excreted from the body, chiefly after oxidation to sulphates, in which form the substance is less toxic. In the process of elimination through the kidney a degree of local irritation is produced, leading to nephritis with necrosis, conditions that develop particularly in prolonged or chronic poisoning.

On account of the toxic action of phenol it is of peculiar value as an antiseptic and disinfectant. For surgical antisepsis from 3 to 5 per cent. solutions are used, though the stronger solutions must be guarded from too prolonged contact and too excessive absorption. Most bacteria readily succumb to these strengths of carbolic acid, but some species, especially anthrax, in particular the spores, are peculiarly resistant. For local cutaneous antisepsis it is now the practice to use concentrated phenol for a few moments of contact, then wash off the phenol with 95 per cent. alcohol.

As a disinfectant for sputum, excreta, etc., 10 per cent. phenol is used, leaving the material to be disinfected in contact for several

hours. This will kill all but the most resistant spore-forming bacteria, and these can be killed by prolonging the contact with phenol.

II.

SALICYLIC ACID AND THE SALICYLATES.

I.

Details of Pharmacological Action.

1. **Toxicity to general protoplasm.**—The salicylic acid group is relatively very much less toxic than phenol. The substitution of a carboxyl radicle leads to a great decrease, but far from a loss in irritant properties of the compound. Therefore these compounds are much more mildly toxic to animal tissues than the phenol, from which they are derived, but are none the less valuable as antiseptics. Solutions of 0.1 to 0.2 per cent. are ordinarily sufficient to prevent the growth of bacteria. The more undifferentiated types of protoplasm are also more strongly influenced by salicylic acid and the salicylates.

Salicylates in the body, presumably due to their initial stimulating effects, lead to an increase in the number of leucocytes, a factor that is by some thought to be the explanation of the favorable activity of these compounds in the clinical treatment of rheumatism.

2. **On the central nervous system.**—Salicylic acid in contrast with phenol is more stimulating and less depressant to the centers of the brain and cord, hence its action is more in line with that of the antipyretics than is phenol. In fact the salicylates formerly enjoyed a popularity as antipyretics, a position dependent upon the depression of the thermogenic center and their toxic influence on tissue metabolism in general.

Hanzlik,¹ who has studied the toxicity of the salicylates, states that when salicylate is given in doses of from 10 to 20 grains per hour signs of toxicity appear after from 180 to 200 grains. "Toxicity is indicated by the appearance of headache, nausea, vomiting, ringing in the ears or deafness, rarely delirium and hallucinations, and sometimes diarrhea." The toxicity is somewhat greater with other salicylates, as indicated by the table below.

¹ Hanzlik, Paul J.: *Jour. American Medical Ass'n*, Vol. LX., p. 957. 1913.

TABLE I

The Mean Toxic Doses of the Various Salicylates (Hanzlik).

Drugs.	Mean Toxic Dose (gr.)
Synthetic sodium salicylate.....	180
Natural sodium salicylate.....	200
Methyl salicylate (oil of gaultheria).....	120 minims
Acetylsalicylic acid (aspirin).....	165
Salicylosalicylic acid (diplosal).....	100

The average dose given in the table is for adult men. For women the toxic quantity is 80 per cent. of the above, i.e., proportional to the difference in weight.

3. On the circulatory system.—The salicylates depress the circulatory system. This occurs from the fact of toxic depression of the vasomotor center on the one hand, and the direct deleterious influence on the muscles of the blood-vessels and of the heart on the other. Acetyl salicylic acid, for example, produces practically no favorable change in the contractions of the frog heart, but when the drug is sufficiently concentrated (0.001 per cent.) slows the rhythm and ultimately to the point of complete suppression. In perfusion experiments the cold-blooded heart may be revived, but only after a long latent period, much longer than required for most drugs of this type tested by physiological assay. It is inferred that this toxic action is a factor in the toxic picture in therapeutic practice.

4. On the alimentary canal.—Salicylic acid and the salicylates are readily absorbed from the alimentary tract. They are slightly irritant to the mucous surfaces and interfere to a degree with the normal digestive processes, owing to the fact that they lower the efficiency of the chemical processes in digestion, 1 per cent. solution decidedly diminishing the enzyme action of the digestive ferments. The nausea and vomiting after salicylates are largely of central origin. Waddell¹ says that vomiting is an early symptom in cats, occurring in from 20 to 90 minutes after salicylates by the mouth. He found that "Emesis follows on hypodermic injections of salicylates after a latent period of at least 20 minutes." Salicylates were not found in the vomitus, a fact greatly strengthening the conclusion as to central origin of the disturbance. The emetic dose for cats is given as 0.6 grm. per kilo of body weight, the toxic dose, 0.9 to 1.1 grms. per kilo in cats.

¹ Waddell, J. A.: *Archives of Internal Medicine*, December, 1911.

5. The antipyretic action.—The simple salicylates are distinctly antipyretic, though not so valuable as the acetanilide series. Their action is multiple. The thermogenic center is markedly depressed, thus lowering the general heat production in the body. At the same time there is a stimulation of the sweat producing glands in the skin associated with cutaneous vascular dilation, thus decidedly increasing heat dissipation.

6. Acetyl-salicylic acid.— $C_6H_4O(CH_3CO).COOH$. (aspirin). This compound "acts like salicylic acid, over which it possesses the advantage of producing less of the undesired local and systemic side effects, on account of the slow liberation of the salicylic acid. It is said to pass the stomach unchanged, the decomposition beginning in the intestine."¹

Acetyl-salicylic acid has distinct toxic properties indicated by its influence on the nervous system. The therapeutic dose occasionally produces distinct dizziness, weakness, and sometimes fainting. Idiosyncrasy is sometimes present, and clinical cases are reported where a single five-grain dose has led to marked cyanosis and edema. The drug produces a depression of the efficiency of the circulatory system with a great weakening of the activity of the heart. The perfused frog heart retains its usual sensitiveness to vagus regulation, even when the cardiac muscle is on the point of yielding its rhythm, which it does to a concentration of 0.001 per cent. in the usual artificial perfusion solutions.

This compound also has the usual amount of antiseptic power and is said to be more readily borne by the body than other forms of the salicylate series.

II.

Condensed Summary of the Action of the Salicylates.

Salicylic acid and the salicylates are less corrosive than phenol and its hydroxy series. Salicylic acid is also readily absorbed into the general circulation, and produces a slight degree of local irritation, but no corrosion of the absorbing surface. The systemic effects are those of a mild stimulation, followed by prolonged depression and mild narcosis. On the central nervous system this leads to a decrease in the reflex sensibility, particularly of the higher centers of the cortex. There is depression of the thermogenic center as well

¹ New and Non-official Remedies, p. 225, 1914.

as of the peripheral heat producing mechanisms, hence the salicylates are of importance as antipyretics. The initial therapeutic action on the circulation is to slightly increase blood-pressure. This is partly due to an increase in vasomotor tone through the regulating nerve centers. The later effects are just the opposite because of the narcosis of this nerve center. There is a toxic depression by direct muscular action on the heart. Respiration is at first slightly increased, followed by depression in both the amplitude and rate. These changes are due to a narcosis of the respiratory center.

The salicylates are used to produce a degree of germicidal action within the body, and their presence is specifically detrimental to the growth and development of the species that lead to the production of rheumatism, in which disease the salicylates have their greatest therapeutic application.

I. Internal Secretions.

CHAPTER XXXI.

INTERNAL SECRETIONS OF THE THYROID AND PARATHYROID GLANDS.

General Introduction.

The internal secretions are defined as those substances which are produced in the body by special glands or gland-like structures and are discharged into the lymphatics or the circulation, ultimately in some way to influence metabolic processes in other tissues of the body. As a matter of fact, all the tissues elaborate materials either pure wastes on the way to elimination or intermediary products, which may be further oxidized, and therefore influence reactions in other parts of the body. Strictly speaking, the waste products are not considered in the class of internal secretions. The term is rather limited to materials which have more specific relations to the functions of other parts, relations that are drug-like in character.

The manner in which internal secretions act in different organs has been under discussion for many years, and it can scarcely be claimed that the matter is at present fully determined. The two leading hypotheses are: First, the theory that the secretion removes or renders inert some toxic substance of the body, and second, the theory that the internal secretion contains some specific substance which is necessary to the normal reactions occurring in other parts of the body. The former has been gradually displaced until at the present time it is practically abandoned. Those internal secreting glands and organs which produce substances that have been isolated and chemically identified by their physiological reactions in the body, have been specific enough to bring them within the second class. One need only to mention the active epinephrine from the suprarenal body as an example.

An ideal internal secretion therefore would be one to which the tissue of some part of the body has become biologically adapted so that its normal function depends on the presence of the secretion. The general physiological assumption is that such internal secretions

contain a particular and more or less specific substance. To substances of this class Starling¹ has applied the name hormone.

Of the glands that are known to produce internal secretions, only a few have had the specific hormone identified. In fact, only two glands, the thyroid (with the parathyroid) and the suprarenal, have had their hormones isolated and identified chemically. However, we may confidently expect as a result of further investigation that additional hormones will ultimately be isolated and their functions more specifically circumscribed.

The subject of internal secretions is at present one which concerns the borderland between Physiology and Pharmacology. This is undoubtedly due to the fact of our incompletely developed knowledge of the actions of the hormones produced by these glands. That the subject will become more and more intensely vital to pharmacology is self-evident, hence its introduction in this discussion at the present time.

The organs which produce internal secretions form a rather extensive list, as follows: Thyroid, parathyroid, hypophysis, thymus, suprarenal cortex, suprarenal medulla, chromaffine tissue, pancreas, liver, kidney, duodenal mucosa, also different portions of the reproductive organs and reproductive tissues, including the testis, ovary (i.e., the Graafian follicle, and especially the corpus luteum), placenta, and fetus.

A.

THE THYROID AND THYROIODIN.

I.

Historical and Chemical.

The thyroid glands, apparently including the parathyroid, have been shown to contain the iodine compound, which was isolated in 1895 by Baumann.² This substance he purified and analyzed, and found that it contained as much as 9.3 per cent. of iodine (0.01 to 0.9 per cent. of the dry weight of the human thyroid). Baumann's thyrioidin is readily soluble in dilute alkalies, but insoluble in acids.

¹ Starling, Ernest H.: Croonian Lectures, 1905. Also *Lancet*, Pt. 2, p. 579, 1905.

² Baumann, E.: Hoppe-Seyler's *Zeitschrift für Physiologische Chemie*, Vol. XXI., p. 319, 1895-96.

It contains from 0.4 to 0.5 per cent. of phosphorus. Thyroidin has been found in both the thyroid and parathyroid glands, though some question still exists as to the accuracy of the determinations for the parathyroids.

II.

Outline of Pharmacological Action.

1. *The thyroid extracts and thyroidin produce changes in metabolism especially affecting the nervous system and the oxidative processes.*

2. *The elimination or removal of the secretion deranges normal metabolism, especially of the nervous tissues.*

III.

Details of Pharmacological Action.

1. **The effects of the removal of the thyroids.**—The establishment of the function of the internal secreting glands in general has been no easy task. Of the earlier experiments in this field the most satisfactory results have been given by two methods. First, that which depends upon the disturbance of bodily functions after the removal of the gland, and second, the changes in function observed upon administering extracts of the gland. In the case of the thyroid, the later studies have shown that many of the brilliant earlier works were vitiated by a failure to recognize the presence of the parathyroids. Gley¹ called attention to the extreme importance of the parathyroids, a point of view that has been fully confirmed since. Vincent and Jolly² state that the removal of all four parathyroids, as well as the thyroids, is not necessarily fatal. Although a fatal outcome usually follows, such is not due to surgical injuries to the surrounding structures, hence must be attributed to the loss of the glands. If the thyroid is removed, the parathyroids apparently are capable of replacing to some extent the characteristic thyroid structure, a deduction based on the change in histological appearance, including the development of colloid. The removal of the thyroids is characterized by a marked myxedema, a condition that also characterizes certain thyroid diseases. The removal of the parathyroids, on the other hand, generally leads to the early death of the animal,

¹ Gley: *Comptes Rendus de la Société de Biologie*, p. 843, 1891.

² Vincent and Jolly: *Journal of Physiology*, Vol. XXXII., p. 651.

preceded by very characteristic nervous muscular disturbances described under the name of thyroid "tetany."

Edmunds has observed thyroid myxedema in monkeys, though this was not confirmed by Vincent and Jolly. The fact that the two internal parathyroids are deeply imbedded in the lobes of the thyroid and are highly vascular makes it exceedingly difficult to remove the one gland without interference with the other. This statement applies in explanation of certain criticisms which have arisen as regards the source of the thyroiodin.

2. **The engrafting of the thyroid tissue.**—In the operative work for the removal of the glands it has been noticed that if an exceedingly small remnant is left behind, the usual symptoms do not follow. In other words, a remnant is capable of taking care of the function of the whole gland. This fact has led to attempts to engraft thyroid tissue in other parts of the body. These attempts, though at first unsuccessful, have finally succeeded. McPherson records beneficial results in man from transplantation of thyroid to the extent that symptoms of myxedema disappeared after operation and had not returned within three years. The transplanted thyroid tissues are usually absorbed, but if they "take" and the vascular supply becomes well established, it is assumed that the normal production of the active thyroid hormone occurs.

3. **The interrelationship of the thyroids and the parathyroids.**—Numerous experiments point to an intricate functional relation between the thyroids and the parathyroids. The most importance rests upon the physiological fact that the removal of the parathyroids is far more fatal than the removal of the thyroids, and that the loss of either of the glands leads to a different type of functional defect from that which characterizes the loss of the other. The embryological and histological observations show that the parathyroids take on the structural characteristics of the thyroids after the removal of the latter, showing a close relationship between the two. The iodine content varies greatly in the thyroid tissue. There is, according to Gley, many times more iodine in the thyroid tissue than in the parathyroid. However, Mendel¹ has confirmed the presence of iodine in the parathyroids. The facts observed have led to the view that the parathyroids prepare the iodine compound, which is later stored in the tissue or colloid of the thyroid. This view of Gley has been strengthened by the observation that there is a disturbance of iodine metabolism when the thyroid is extirpated.

¹ Mendel, L. B.: *The American Journal of Physiology*, Vol. III., p. 263, 1900.

4. **Observations from the feeding of the thyroid tissue and of thyriodin.**—Experimental procedure demonstrated the stability of the thyroid hormone, both to digestion and to heat, even before the isolation of thyriodin. Now both thyroid tissue and the thyriodin are given by way of the mouth. Thyroid substance introduced

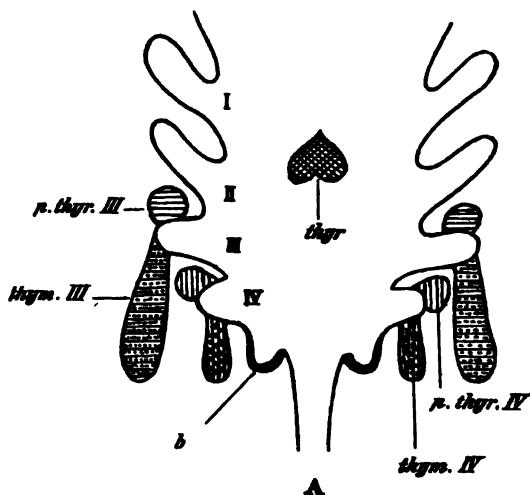


FIG. 63.—Diagram to show the branchial origin of certain internal secreting glands. I, II, III, IV, the respective branchial arches; *thyr.*, thyroid; *p. thyr.*, parathyroids; *thym.*, thymus; *pb. b.*, post-branchial body, which in development becomes imbedded in the thyroid. From Vincent and Jolly.

by this channel has the same physiological effects that occur from engrafting the tissues. It would seem that the active hormone is not only not destroyed in digestion, but is absorbed and can reach the circulation and thus influence metabolism in the usual way. Thyriodin purified by the method of Baumann is recommended as a substitute for the thyroid tissue. While the influence which it has on metabolism seems to be the same, it has not always proved to act with the same vigor and efficiency as the tissue of the gland itself. Certainly iodine, as such, does not take the place of this organic thyriodin compound, hence it is assumed that the function of the gland is to build up the thyriodin compound, thus getting the iodine in an available form for the use of other tissues.

In confirmation of the point just made, Marine has found that enlarged thyroids with a diminished quantity of thyriodin present tend to return to the normal upon feeding of iodine. After iodine he found an increased percentage of thyriodin present in the gland. In other words, as Marine expresses it, "iodine administered to dogs

with hyperplastic thyroids has a physiological action like the desiccated thyroid, i.e., it rapidly reduces the body weight, while iodine administered to normal dogs does not."

B.

PARATHYROIDS.

We have already stated the fact that the removal of the parathyroids without interference with the thyroids leads to grave symptoms and usually the death of the animal, though, as was stated above, Vincent and Jolly showed that death did not always follow.

5. **Systemic phenomena following removal of parathyroids.**—In a word, the typical symptoms following the removal of the parathyroid is expressed by the term "tetany." The animals show a progressive development of nerve and muscular incoördination, ending in tetanic spasms and death. There are evidences of central nervous disturbances expressed in the restlessness, anxiety, and mental stress as interpreted from operated dogs.

6. **Disturbances of metabolism after parathyroidectomy.**—W. F. Koch¹ has recently examined the effects of parathyroidectomy on dogs from a physiological chemical standpoint. He found the presence of methylguanidine in the urines of six different animals investigated, as well as certain other purine derivatives. After parathyroidectomy, Koch's dogs died in four or five days, exhibiting the usual muscular and nervous spasms, i.e., "tetany."

The chemical showing was supplemented by a study of the histological changes in different tissues. Material from the liver, kidney, and brain showed cellular chromatolysis as a constant characteristic. "The brain sections showed cells in the motor areas with partial loss of Nissl substance and typical tetany nuclei. Various degrees of chromatolysis were also observed in these nuclei." He found degenerating epithelial cells in the intestinal tract, the nuclei of which were converted into solid, deeply staining clumps.

The hepatic cells "showed advanced fatty degeneration of the protoplasm. The nuclei of large areas had disappeared entirely in places where the cell form was fairly well preserved." In the liver of certain of his animals there was only a diffuse chromatolysis. In the kidney there was "congestion and hemorrhage in the cortex, some anemic and others congested medullæ. Some glomeruli had lost Bowman's capsule." There was also epithelial degeneration.

¹ Koch, W. F.: *The Journal of Biological Chemistry*, Vol XV., p. 43, 1913.

Physiologically the dogs were restless and easily excited. The limbs later "showed tremors, especially after slight exertion." Still later the animal exhibited mild convulsions with rigid and extended limbs. In the final stages before death, there were "severe tetany and clonic convulsions," and at times salivation and Cheyne-Stokes breathing.

7. The theoretical significance of Koch's observations.—The discovery of toxic bases, methylguanidine and other guanidine bases, in large quantities in the urines of parathyroidectomized dogs has led Koch to believe that "the parathyroid secretion, therefore, appears to be concerned with anabolic processes closely related with the building of nucleins." Koch comes to this conclusion from the pathological appearance of the tissues, i.e., their chromatolysis, along with the finding in the excretion of the wastes undoubtedly derived from nuclein metabolism. It is generally conceded that the metabolism of chromatin is a nuclear function. The failure of different functions in the parathyroidectomized animals drives the tissues to protein starvation and "nuclein atrophy." This is peculiarly suggested by the extensive coagulation of the blood in the blood-vessels, and indicates the presence of free nucleic acid in the circulation.

In what manner the absence of the parathyroid leads to this marked tissue disruption remains yet to be explained. The work of Koch brings us much nearer the solution of the problem, since it gives for the first time an explanation of the nature of the change in metabolism. It has not yet been shown that the artificial supply of parathyroid substances will alleviate this condition.

CHAPTER XXXII.

THE PITUITARY GLAND AND THE HYPOPHYSIS.

I.

Anatomical.

The pituitary anatomically consists of three parts: (1) the pars anterior, or pituitary gland proper, (2) the pars intermedia, which is distinctly separated from the anterior and more closely related to (3) the pars posterior or hypophysis proper. The anterior and intermedia portions are derived from the epithelium of the roof of the mouth, while the hypophysis is an evagination of the brain cavity. That these two structures produce internal secretions or hormones can no longer be doubted, though a chemically distinct hormone has been isolated from neither.

II.

Outline of Pharmacological Action.

1. *The evidence indicates that the pituitary increases oxidation and stimulates the growth of the connective and skeletal tissues.*
2. *The internal secretion of the pituitary has a reciprocal relation to the development of the essential sexual organs.*
3. *The hypophyseal extracts (posterior lobe) produce an increase in the force of the heartbeat, the contractions of the smooth muscle structures, such as the bladder, uterus, and intestine, increase in carbohydrate metabolism, and an increase in certain secretions.*

III.

Details of Pharmacological Action.

A. Pituitary Gland.

1. **The changes in metabolism following the removal of the pituitary secretion.**—Our knowledge of the pituitary is largely derived through observation of changes in function or in growth, which accompany atrophy of the gland or its removal on the one hand, or

the contrary changes that are associated with hypertrophy of the gland, or with the injection of its extracts.

As in the case of the interrelation of the thyroid and parathyroid, so here the mechanical difficulties of separating the pituitary from the hypophysis have contributed largely to the difficulties in determining the function of these two important structures.

Recently, through the skill of such investigators as Paulesco, and of Cushing, operations have been performed, removing the anterior or the posterior lobes independently. When the pituitary gland proper is removed, as a rule death soon follows. This can now be recorded as an established fact. The inference offered in explanation is that the disturbing cause is the elimination of the interstitial secretion of the gland.

The removal of large portions of the pituitary gland, and in some cases of the entire gland, in early life is survived (three-months-old puppies). However, there is a restriction in the usual growth of the body with certain changes in the general tissues, particularly in the acquirement of fat. The reproductive organs also fail to develop and show atrophic changes. Metabolism experiments on such animals show a diminution of oxidative processes, especially characterized by a lesser amount of carbon dioxide.

2. **The administration of pituitary.**—Numerous attempts have been made to resupply the pituitary, experimenting along the lines which have long been practiced in the case of the thyroid. Schaefer, and later Cushing, have published numerous observations. Both have fed pituitary and reported that the symptoms which follow the removal of the gland are delayed by this treatment, a fact, however, which has not been always supported. Cushing, in particular, finds that patients suffering from diminished pituitary secretion are benefited by the pituitary extracts.

Transplantation of anterior lobes was performed by Cushing in an animal from which this lobe had been removed. This delayed for several weeks the fatal results that usually follow the operation.

3. **Clinical evidences from atrophy and hypertrophy of the pituitary.**—It has been long known that certain individuals have manifested retarded development on the one hand and an extraordinary development, acromegaly, on the other. The explanation of these exceptional cases seems now definitely traced to the variation in development of the pituitary gland. A hypertrophied gland so stimulates the growth of the bony tissues as to produce an enormous size of the body. On the other hand, atrophy of this organ leads

to the opposite result, namely, infantilism. It is in this latter class that Cushing has attempted to secure benefit by giving the gland in routine medicinal treatment.

4. **The interrelation of the pituitary and other organs.**—There is a reciprocal relation existing between the pituitary and the thyroid. The operative interference with the thyroid, as by removal, is associated with a vigorous "taking on" of its function by the pituitary, as manifested by the greater size of the latter. On the other hand, a much more important interrelation exists between the development of the pituitary and the sexual gonads. This has already been mentioned. In dogs, the development of the ova and spermatogenesis are markedly delayed by removal of the gland, whereas an accelerated sexual development has marked certain cases of giantism.

B. Hypophysis.

1. **Influence of the hypophysis on the functions of nerve structures.**—The hypophysis bears a less crucial relation to the body functions than does the pituitary. The extracts of the gland, however, have been demonstrated to produce definite changes in the physiological function of organs of the circulatory system, of the digestive tract, and of the uro-genital system.

2. **The heart.**—Howell first clearly demonstrated that the posterior lobe, which he called the infundibulum, has a marked influence on the circulatory apparatus. The injection of the extracts produces a rise of blood-pressure, with an initial acceleration of the heartbeat. This was followed by some depression of blood-pressure, and there was a marked slowing of the heart rhythm. It has been shown lately that the stimulus to the heart action probably rests on stimulation of peripheral augmentor nerve structures.

3. **On smooth muscular structures.**—The digestive tract is stimulated to increased contraction by the intravenous injection of hypophyseal extracts. The uterus undergoes excitatory contractions probably through the stimulation of nerve structures of the inferior mesenteric paths. These paths also supply nerve fibers to the urinary bladder, in which increased contraction is also noted.

4. **Hypophysin.**—The name "hypophysin" has been given to the active principle or extract of the hypophysis or posterior lobe. The true source of this active material is not altogether clear, since the colloidal material found in the pars intermedia and to some extent in the hypophysis may be of extraneous origin so far as the hypo-

physis is concerned. It is generally conceded that the secretion of the pituitary is distributed into the spaces of the pars intermedia and the pars intermeninges. It is possible that this secretion may pass into the hypophysis to some extent. By this view one may readily understand the fatal outcome of the removal of the pituitary in that it removes the active tissue forming this internal secretion. The removal of the hypophysis would not interfere with the development, but only with the distribution of the pituitary secretion.

J. Irritants and Counter Irritants.

CHAPTER XXXIII.

THE BACTERIAL TOXINS.

General Introduction.

There are a great many drugs and materials of general pharmacological interest, the importance of which is chiefly bounded by some local and special action, i.e., a local toxic action to protoplasm, which is associated with more or less profound secondary changes. Some of these lead to a quick dissolution of protoplasm, hence are corrosive in nature. Certain of these drugs are discussed in other connections, i.e., the caustic alkalis and the mineral acids. In this entire group, even with drugs in which the caustic action is very intense, some degree of their influence generally calls forth a response in the tissues characterized by the process of inflammation. Such drugs are called **Irritants**.

The number of chemicals and other agents which produce injury, therefore irritative processes, is enormous, hence it will conserve the time of the reader if the principles underlying their action are briefly explained and illustrated by typical members of the series.

Irritants may act on any and all tissues of the body or on special structures only. Therefore, the groups of irritants, which we shall emphasize, are of necessity somewhat arbitrarily chosen. They are of four great classes:

1. The Bacterial Toxins, reacting on any and all tissues of the body with which they come in contact, but often quite specific in the case of particular toxins.
2. The Skin Irritants, those drugs generally recognized because they are peculiarly adapted to affect the relatively impermeable external skin.
3. The Vegetable Cathartics, that large group of irritant preparations of vegetable origin, which react on the lining of the alimentary canal and which are used in clinical medicine for the production of catharsis.

4. The Counter Irritants, those drugs primarily of groups 1 or 2, which, in a certain intensity of action, produce marked secondary changes in other parts of the body. Reactions of this class are known in medicine as counter irritations and the causal agencies as counter irritants.

I.

Historical and Introductory.

It is difficult to condense into a few words the essential factors in the discoveries and study of the influences of bacteria and bacterial products on the living organism. This topic is at the foundation of our study of the Germ Theory of Disease, and its fundamental importance permeates a number of essential medical subjects. Bacteria growing in the living body may in themselves through mechanical factors induce stages of inflammation. However, this is quite a secondary influence in contrast with degrees of change induced by what we now know to be chemical substances liberated by such bacteria during their life cycle.

Bacteria induce chemical changes in proteins, setting free toxic disintegrative, i.e., putrefactive substances. These substances are basic in character and have received the class name ptomains. They also produce synthetically and liberate in solution in the circulating fluids a different class of non-basic poisonous substances, which are called toxins. Certain bacteria finally at the time of disintegration after their death liberate yet a third class of toxic materials similar in character to the toxins but less soluble, known as endotoxins.

The influence of putrefactive products developed in decaying flesh was first experimentally examined by the physiologist, von Haller, in the eighteenth century. In the middle of the nineteenth century Panum examined these substances for their physical and chemical properties, and gave us some notion of their toxicity by experiments on dogs.

Breiger in the period from 1882-1886 isolated and determined the chemical context and composition of a number of toxic substances derived from decaying meats. Among others are trimethylamin $N(CH_3)_3$ and mytilotoxin $C_6H_{15}NO_2$, from the poisonous mussel. The non-basic poisonous substances, which we now call toxins, were in Brieger's scheme of classification named toxalbumins. These toxins have been extensively studied, but not chemically isolated. Toxins, as above defined, do not cover all the toxic substances resulting from

bacterial growth. It is found that the dead and disintegrating cell bodies of certain bacteria contain highly toxic but less soluble materials than the toxins. These are the endotoxins. Neither have the endotoxins been chemically isolated.

When toxic bacteria are growing in the living body, or in fact, when the toxins derived from their growth are injected into the circulation, the body tissues are stimulated to produce chemical substances which are neutralizing to the toxins. These are the antitoxins first described by Behring and Kitasato¹ in 1890. The formation of antitoxins does not include all the protective processes induced by toxins in the animal body. The studies of Pfeiffer in 1894 on immune cholera serum developed the fact that the serum contained a destructive agent, which we now know under the name bacteriolysin. Without going into detail, attention may be called to the agglutinins and precipitins, which, together with the lysins and antitoxins, contribute to the immunity of an animal against bacterial invasion.

II.

Details of Pharmacological Action.

1. The nature of irritant action.—An irritant, mechanical or chemical, may be defined as an agency which produces a local injury, to which the tissue or tissues react by a reconstructive process, the stages of which constitute acute inflammation. That the drugs of the so-called "Irritant" series possess toxic action for most tissues of the body is a well-known fact and does not need elaborate discussion, but the character of the action of the irritant calls for detailed explanation. Chemicals are by no means the only agencies for the production of irritations leading to inflammation. One of the simple causes of the inflammatory process is ordinary mechanical injury, i.e., traumatism. The redness or the blisters from milder burns are responses to heat irritation. Excessive nerve reactions may produce similar end results. Bacterial growths, certainly of the infectious and often of the saprophytic type, set up inflammations, due chiefly to chemicals in this case, however. The products of bacterial growth, toxins, are typical irritants, though the discussion of their action because of the great importance in relation to the cause of

¹ Behring and Kitasato: "Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren," *Deutsche medicinische Wochenschrift*, p. 1113, 1890.

disease is now studied in more advanced detail in other medical relations. The response to irritation, i.e., inflammation, may, in fact does, occur in all parts of the body and in all tissues. In the broader sense it is obvious that no logical boundary between susceptible and non-susceptible tissues can be drawn. But in the restricted sense, in which the term is more often used, pharmacological irritants are primarily either skin irritants or irritants of mucous membranes.

2. **The inflammatory process a physiological response to irritant action.**—The basic principle to consider in the study of irritants is the fact that they are injurious to protoplasm of all kinds. Of course different drugs of the various classes injure in different degrees, therefore the degree of the response which is produced will depend on the relative toxicity of the drug as such, or on the relative toxicity as influenced by its time of contact, or by its concentration. The protoplasmic factor is the sensitiveness of the tissue to local injuries. Of all the tissues, the epidermal and the connective tissues are especially responsive to toxic actions of this class. Toxins are only chemicals of a special class.

The mild action of practically all irritants can scarcely be distinguished from that of physiological stimulation, which indeed it is. There is no sharp line to be drawn between the physiological meaning of the two terms. If any distinction is to be made, it is the tendency to apply the term "irritant" to causes of reactions which are in the nature of general responses of protoplasm, or perhaps it would be better to say responses of general protoplasm. The word "stimulus" in contradistinction to this use is applied to causes of reactions expressed through the more highly differentiated organs and tissues, and by the characteristic power which the special tissue possesses by virtue of its differentiation. To illustrate further, the stimulation of a muscle calls for the characteristic contraction. This may be with or without a general change in the protoplasm of the tissue. Irritation applied to a muscle, while it may lead to contraction, has a tendency to produce basic changes in the protoplasm itself, which, if carried far enough, may lead to disintegration with destruction of the tissue. Speaking generally, the incipient irritative process, whether it be produced by drugs or other injurious agencies, is of a stimulative nature. But the reaction tendency in general is that of cell growth, cell proliferation or cell death, rather than that of energy liberation. If the irritation be carried further, then there is injury to the local tissues, which is characterized by definite changes following in a well-described cycle. These are the changes of inflammation that have

been so admirably presented by Adami,¹ Councilman,² and others.

In the section on skin irritants there is presented a detailed description of the process of inflammation as it occurs typically in the skin. This detail should be consulted and is presupposed in connection with the discussion that immediately follows on the irritant action of the bacterial toxins.

3. **The irritant action of bacteria and bacterial toxins.**—Of all the irritative and toxic agents that affect the human body, those of most practical importance are the bacteria and the toxins, lysins, etc., resulting from their presence, growth, and development. Not all micro-organisms have an irritant action on the human body. Many forms of bacteria inhabit the skin, the mouth, and different divisions of the alimentary tract without producing deteriorating effects on those structures, at any rate not under ordinary conditions. Certain bacteria are in marked contrast, the pathogenic bacteria. These are peculiarly destructive to the tissues of the human body.

A great variety of conditions influence and control the rate and character of the invasion of the human body by pathogenic bacteria. Among those that should be mentioned are variation in individual susceptibility, variation in the defensive powers of the individual at different times, the mode of invasion, and the relative virulence of the particular organism concerned. Not all tissues of the body are equally resistant to the invasion of any particular pathogenic bacterium. As a rule, the most highly differentiated tissues are the most susceptible, while the tissues of more generalized function, such as the connective tissues, are the least susceptible.

When pathogenic bacteria invade the body they produce, as a result of their growth and development, materials that are highly irritant and peculiarly toxic to the human body. These substances are the *toxins*. It may happen, however, that the active irritants are not liberated directly by the living bacteria, but are set free upon the destruction of those bacteria that have run their life cycle. These substances have received the name *endotoxins*. In either case the injurious agencies come from the presence of the bacteria, and are strongly disturbing to the normal functional reactions of the protoplasm of the tissues of the host. The liberation of the toxins resulting from the growth of the colony of invading bacteria of course takes

¹ Adami, J. George: Chapter on "Inflammation," *Principles of Pathology*, 2nd edition, New York, Vol. I., p. 413, 1909.

² Councilman, Wm. T.: Article, "Inflammation," *Buck's Reference Handbook of the Medical Sciences*, Vol. V., p. 1, 1902.

place primarily at the growth center, the focus of invasion. They readily diffuse into the blood stream and the surrounding lymph channels, thus reaching a general systemic distribution. We find, therefore, that the toxic action of the toxins is both local and general in nature: local, because of the more intense concentration of toxin resulting in local inflammation; general, because of the ready distribution of toxin through the circulation and its contact with all the tissues.

Bacterial toxins are, in the last analysis, strongly irritant agencies. They produce the cycle of irritation and inflammation, running a course which is more or less characteristic for the different tissues, and for the different toxins. The interrelations have been strongly put by Adami,¹ when he used the action of toxins to illustrate degrees of irritation as follows:—

“Reverting to the differing degrees of irritation, we may draw up a working scale of, for example, toxins. Certain of these, which we will for the moment designate degree A, are so strong that they kill at once a certain cell with which they come in contact; others, degree B, are not strong enough to kill instantly, but they so injure the cell that it enters at once into the stages we call cloudy swelling, granular degeneration, or whatever name we employ, and finally dies; this process we call bio-necrosis. Yet others, degree C, injure the cell so that it enters this condition of successive ill-being, but finally recovers; this is not exactly bio-necrosis, but, if we dare coin a word for present use in this chapter, it might be said that the toxin is bio-necrescent, that is, tending to bio-necrosis. Finally, other toxins, yet weaker, degree D, irritate the cell within the limit of its reactive powers, but without exhausting the same, and its irritation is shown by reproduction, by phagocytosis of chemiotaxis, or any other function we can attribute to the cell that is ‘roused.’ And this is true, not only in regard to different toxins, but in regard to different degrees of concentration of the same toxin. We have to recognize, in short, the law that the agent, which in high dilution or small quantity acts as a stimulant to the cell, becomes in greater concentration a poison to the same.

“It will be at once evident that, in the kidney, for example, toxic blood may severely injure a tubule cell (degree B), yet may not be able to do more than rouse the connective tissue to reproduction (degree D). Every cell of the body that comes within the ‘sphere of influence’ of a toxin reacts, in some degree thereto, degree A, B, C,

¹ Adami, J. Geo.: *Keen's Surgery*, Vol. I., p. 191, 1906.

or D, and this applies, not only to fixed cells, but to every lymphocyte, leukocyte, or wandering tissue cell whose business calls it into the area of irritation at the time; the result of any inflammation depends, therefore, on the sum total of these million tiny problems, and the total determines whether the balance is in favor of or antagonistic to the body."

The broad subject of bacterial toxins and their action has, however, assumed such importance and has become so specialized in relation to disease that the custom has arisen of treating this subject in special texts and monographs,¹ hence the very brief discussion presented in this relation.

4. The characteristics of toxins.—The toxins are admittedly chemical substances, although we know very little of their detailed chemical nature. The great mass of our knowledge of the nature of toxins is derived from the influences of these substances on physiological processes. One point that has come out in their study is that toxins diffuse through animal membranes with great difficulty. Their action on living protoplasm is more or less specific and in this regard there is some comparison between the toxins and the toxic influence of certain proteins, that is, they are capable of stimulating the tissues to the production of antibodies. The toxins are nearly all destroyed by enzymes, by heat, and, in some cases, by light. Chemical substances of analogous composition are found in both the animal and the plant world. For example, the venom of poisonous snakes and of poisonous insects reacts in a way quite similar to the toxins of bacterial origin. In the plant world the poisonous ricin is possibly also of similar nature. At any rate, it produces similar reactions on protoplasm. Recently some most interesting observations that throw light on the nature of toxins have been made on isolated by-products of bacterial putrefactory changes. Barger and Walpole² isolated three pressor principles from putrid meat, namely isoamylamine, derived from leucine, phenylethylamine, derived from phenylalanine, and parahydroxyphenylethylamine, derived from tyrosine. These amines have many of the physiological characteristics of the toxins,

¹ See Vaughan and Novy: *Cellular Toxins*. Philadelphia, 1902.

Schorer: *Vaccine and Serum Therapy*. St. Louis, 1909.

Oppenheimer: *Toxin and Antitoxin*. Jena, 1904.

Ehrlich: *Gesammelte Arbeiten zur Immunitätsforsch.* Berlin, 1904.

Also works on bacteriology, pathology, and on infectious diseases.

² Barger, G., and Walpole, G. S.: *Journal of Physiology*, Vol. XXXVIII, p. 343, 1909.

although the isolation of toxins has not been chemically made and we cannot as yet be sure that they are of the same class. At least one may consider these purified amine bodies as showing interesting analogies as between the pharmacological action of the amino-acids and the toxins. This group is of further interest in that it has been lately shown by Barger and Dale that the same active principles are present in the fungus ergot.

5. **The type of toxin action.**—We get our best conception of the nature of the toxin reaction by comparison of the reactions in the chemical field. Certain complex organic chemicals have a multiplicity of side chains to which other substances may be chemically bonded. This conception has been applied to the toxins of unknown chemical composition by Ehrlich in his Side Chain Theory of the action of toxins and antitoxins. As early as 1885, Ehrlich, in discussing the nature of cell nutrition, expressed the opinion that the great variety of nutrient substances were assimilated by a method of attachment or bonding of these substances to the complex of the protoplasm. In short, protoplasm by means of its numerous side chains was able to chemically attach to itself the materials entering into its nutrition.

This conception applied to the action of toxins resulted in the development of Ehrlich's Side Chain Theory, a theory that wonderfully adapts itself to the explanation of the great variety of general biological and chemical processes as well as those physiological processes involved in toxic action.

6. **Toxins stimulate the tissues to produce antitoxins.**—The presence of toxins in the body affects the protoplasm of the tissues in one highly important way, namely, it stimulates the production of substances which have the general effect of neutralizing or warding off the toxic action of the toxins themselves. The tissues, in other words, produce chemical substances which are antagonistic to the toxins. These are the antibodies and are called antitoxins. Antitoxins were first described by Behring and Kitasato in 1890. These men produced immunity in animals against tetanus by injecting the serum from certain actively immune animals. The presence of a poisonous amount of toxin which, if it ran its course in the body, would result in the destruction of the life of the organism as a whole is rendered relatively innocuous, provided a sufficient quantity of antitoxin can be developed to take care of the toxin. This is the principal factor in the self-limitation of many of the infectious diseases. The development of antitoxins by the body in response to the presence of the toxic bacteria is called active immunization. Medi-

cine has now reached a stage of development in which science has been able to produce antitoxins in usable quantity by injecting certain animals that are relatively immune with the pathogenic bacteria for which the antitoxin is specific. Such serum, rich in antitoxin, when introduced into the body of a person also exerts a restraining influence on the growth or invasion of pathogenic bacteria. This method of securing protection is known as passive immunization.

7. **Specificity of toxins.**—Without discussing the matter in detail, attention may be called to the fact that many of the toxins are notably specific or selective in their reactions among the tissues of the body. As a single example may be mentioned tetanus toxin which attacks nerve tissue. If brain tissue be mixed with a tetanus toxin solution and the brain tissue be separated off, it carries with it the toxin.

When the human body has been attacked by certain bacteria, for example tubercle bacilli, the reaction in the tissues leads to a change in the susceptibility of those tissues to the products of the growth of the bacilli. The tuberculin skin test is an example in this case. The epidermis of the tuberculous patient is more susceptible to the irritant action of tuberculin than the skin of a normal person. This increase in susceptibility is great enough to give to the reaction of irritation a specificity which aids in the diagnosis of the disease.

There is a close relation between the toxin and the antitoxin developed by the body under the influences of the toxin, a relation that is in this instance entirely specific. Each particular toxin stimulates the tissue to produce an antibody, which reacts with and neutralizes the toxin, thus eliminating the latter from its poisonous influences on the body tissues themselves. An antitoxin developed in response to one toxin will not combine with a different toxin. In other words, the antitoxins are not interchangeable in antagonizing the toxins. One can find an analogy in the chemical field as between the reaction of chemical substances which have an affinity for each other, but not for chemicals of a different class. The development of antitoxins by the body is, therefore, a protective factor, a response of the tissues to the irritant and toxic action of the toxins. The reaction between the antitoxin and the toxin is, therefore, a reaction of distoxication. In other words, the toxin is rendered chemically inert by the ever present antitoxin. It is the presence of the antitoxin in the blood and body fluids which seizes upon and fixes any entering toxin irritants and gives to the body the property of immunity.

CHAPTER XXXIV.

IRRITANTS OF THE EXTERNAL SKIN.

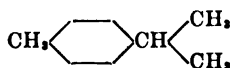
I.

Historical and Introductory.

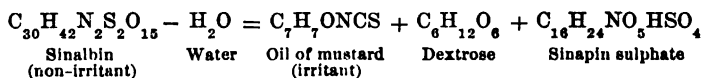
Numerous chemical groups, with a wide range of representation, induce inflammatory changes in the skin. These chemicals possess two properties, which adapt them to this type of reaction in the body, namely, a high degree of toxic influence on general protoplasm and general solubility in the skin fats. The conventional members of this series are:—

1. The essential oil group consisting of the volatile oils, often in solution in the tars and resins; 2. The mustard group containing glucosides which, on cleavage, liberate an irritant oil; 3. The cantharidin group, consisting of soluble and highly irritant neutral bases; and 4. Forms of mechanical energy such as heat, etc.

Turpentine serves as a type of the volatile oil series. This is a distillate from certain woods, especially the conifers, and contains a resin dissolved in essential oils. The various volatile oils belong to the benzine group, and contain numerous representatives of the terpenes with the formula C_6H_8 , or some multiple of this grouping. They are easily converted into cymene, which has the structural formula:—



Members of the genus *Sinapis*, the mustards, contain beside other substances, sinalbin, which is a glucoside, in combination with the oil of mustard. The plant also contains a glycolytic ferment. The pulverized seed of *Sinapis alba* when mixed with water ferments according to the following formula:—



Cantharidin is a very strong irritant derived from the dried beetle, *Cantharis vesicatoria*, of southern Europe. This material

contains the toxic substance cantharidin, $C_{10}H_{12}O_4$. Cantharidin is slightly soluble in water, in alcohol, etc. There are a number of other materials, notably the toxicodendrol of our common American poison ivy, which have similar irritant actions.

Mechanical agencies such as heat are skin irritants. Heat, for example, may be applied in so many different ways and under such well controlled circumstances that it becomes one of the best of practical agencies for inducing degrees of irritant action for therapeutic purposes.

II.

Outline of Pharmacological Action.

1. *Power to penetrate the corneal layer of the outer skin and produce varying degrees of toxicity to the underlying epidermal tissues, nerve endings, etc. Or, in the case of heat, power to produce direct mechanical injury and irritation.*

2. *Power to produce counter irritant effects on account of the peculiar segmental nervous relations of the skin and the deep-seated organs.*

III.

Details of Pharmacological Action.

1. **The permeability of the skin to certain irritants.**—The general resistance of the external skin to large classes of injurious substances renders it more or less immune to many agencies which would induce inflammation if brought into contact with unprotected parts of the body. This is primarily due to the relative impermeability of the skin to chemical agents. Members of the volatile oils and others of the chemicals mentioned above more freely penetrate the corneous coat of the skin and reach to the living epidermal cells and the dermal structures below. In addition there are certain highly volatile chemicals, like chloroform, which are soluble in the skin and which if held in contact with it a sufficient length of time produce irritation. Under ordinary conditions the great volatility prevents the manifestation of their irritant properties. Irritant substances, on account of their ready diffusibility through the corneous layer of the skin, or by virtue of their solubility in some particular constituent of the skin, can readily penetrate this otherwise impervious structure. These materials are injurious to protoplasm and set up changes which are described by the various stages of the process of inflammation.

2. **Stages of acute inflammation produced by irritation.**—Inflammation of the skin is characterized by the development of reddening

ing, swelling, heat, and pain, i.e., the "rubor, tumor, calor, and dolor" of Celsus. There is naturally a varying degree of disturbance of the function of the part. It is a well established physiological fact that a very mild cutaneous stimulation generally, though not always, leads to a slight vascular constriction, i.e., a heightened vascular tone which in the skin leads to the external manifestation of pallor, etc. If, on the other hand, the stimulation is vigorous, approaching the painful, the response leads always to vascular dilation.

Skin irritants produce more than simple stimulation, but we may expect the same physiological reactions from the mild local nerve effects of the irritants. These irritants act through a period of time and with increasing intensity. Hence the reaction on the circulatory system, while it may at the very first show vascular constriction, will later lead to marked dilation of the blood-vessels of the part affected. It is this process that especially characterizes the first stage in inflammation, namely, the reddening of the skin with local increase in temperature.

If the irritation is mild, the great increase in the flow of blood through the part, other things being equal, will tend to eliminate the irritating chemical or other agent, thus fulfilling the biological function of the response and stopping the pathological process. Hyperemia favors physiological oxidation and the normal metabolism of tissue per unit of time. The increased volume of blood also brings a greater amount of oxygen in contact with the tissue at this stage, a reaction that would favor, not only the washing away of the injurious substances, but in some cases its oxidation and destruction. The physiological correlations induced by anemia and hyperemia are very important in this connection, topics that have been recently clearly and elaborately presented by Guthrie¹ in his book, *Blood Vessel Surgery*.

The second stage of irritation is characterized by swelling, edema, blood stasis, and a great gathering of the migratory and phagocytic cells. This is associated with more or less acute pain and sensitiveness of the involved local area. Briefly stated, the successive changes are: the gathering of white blood corpuscles along the walls of the dilated blood-vessels, soon followed by ameboid migration of these cells through the vascular endothelium and through the connective tissue and lymph spaces. It is apparent that the resistance of the endothelial tissue is reduced and that the ameboid response of the white blood cells and lymphocytes is increased. This stage is accom-

¹ Guthrie, C. C.: *Blood Vessel Surgery*, p. 132. New York, 1912.

panied by or followed by a corresponding increase in the amount of the exudations so that the plasma passes through the vascular walls, greatly increasing the extra-vascular fluid and producing the swelling or turgor of the part. In many local irritations, this process may be so strongly accentuated as to produce accumulation of fluid under such tension as to lift the corneous layer, forming vesicles or blisters. The fluid of the vesicles may contain the irritant agent



FIG. 64.—Gathering of white corpuscles in capillaries of an inflamed area. 1. Adhesion to capillary walls. 2. Migration through the wall. From Lavadovsky.

in solution. In the later stages of the diffusion there is stasis of the red blood corpuscles with extravasation. The movements of the lymphocytes and of the various white corpuscles is undoubtedly a chemiotactic response. Not only do these cells gather in large numbers in the inflamed tissues, but they may and often do actively multiply so that their numbers are enormously increased.

When the action of the irritant is extraordinarily severe there follows death of the protoplasm of many of the cells and the phenomenon of suppuration with disintegration takes place. This latter type of response is characteristic of that called forth by certain infectious organisms. Here there may be an enormous increase in the number of phagocytic cells especially of the polymorphonuclear type. The irritants of the class therapeutically called pustulants produce this type of inflammation. The pus discharged consists of the excessive accumulation of corpuscles together with the disintegrating product of the dying tissue cells.

One can distinguish at least three stages in the process between the incipient irritative action and actual cell death. These stages may be, though they are not always, called forth by the continued action of a strongly toxic irritant. The action may be mild and reach only the first stage, as, for example, *simple inflammation*. If the action is more vigorous and rapid, then the inflammation is followed by or reaches the stage of *vesication*. In other words, the edema may reach a point where there is an accumulation of lymph, therefore *vesicles*. The irritants may finally lead to a fatal termination in the tissue of the local area, for example, in the case of excessive cell disintegration, i.e., *pustulation*. In this final or fatal termination, of course the body has failed in the response which would ordinarily meet the injury of the irritant.

Where degeneration is only partial and the injurious agent is removed, a definite recuperative process takes place. Or if, as in the case of certain bacterial infections, its further action is prevented or at least diminished by a process in which the agency is walled off by constructive growth changes about the area of the infected focus. These reconstructive changes belong to the provinces of pathology, and the reader is referred to the extensive literature of pathology and bacteriology for its further description.

3. **The irritant action of the volatile oils.**—The most important of the volatile oils are oil of turpentine, oil of pine, oil of juniper, Canada balsam, and myrrh. Several other substances, the most important of which is chloroform, have similar action and physiologically could be classed in this group, though chemically they are very different in character. These oils readily penetrate the skin and are irritants of varying degrees of toxicity to the underlying tissue. They act comparatively slowly and are milder in effect than are some of the other irritants, for example, cantharidin.

4. **The toxic glucosides of the mustard series.**—Oil of mustard is a highly irritant material which also readily penetrates the skin. It is derived from different species of *Sinapis*, the most common being black mustard, or *Sinapis nigra*, and the white mustard, or *Sinapis alba*. The irritant oil is present in the seeds of the plant as a chemically inert glucoside. But the seeds contain a ferment which, upon being moistened with water, sets up a fermentive process in the glucoside whereby the actively irritant mustard oil is set free. The reaction proceeds according to the formula given on page 2. This reaction is utilized in the mustard plaster used for medicinal irritation. Ground mustard seed is spread out in a thin layer

which, when moistened, slowly undergoes fermentation. When a mustard plaster is applied to the skin it is at first non-irritant, but as the mustard oil is slowly set free, it reacts on the body to produce inflammation. The longer the material is in contact with the skin, the more intense the inflammatory process, largely because of the accumulating quantity of mustard oil. An active clinical mustard plaster will produce redness and mild inflammation in fifteen minutes, and vesication in thirty to forty minutes in a sensitive skin.

5. Irritants of the cantharidin type.—The highly irritant cantharidin is soluble in oils and alcohol, but is only slightly water soluble though its salts easily pass into solution.

It produces the most violent irritative changes in the tissues of any of the irritants thus far considered. It readily penetrates the skin and sets up local inflammation which produces the vesication. As small a quantity as 0.1 milligram is adequate to produce this effect on the human skin.

The salts of cantharidin very readily pass into the general circulation and lead to vigorous inflammation in other parts of the body, particularly in the kidney, the bladder, and the uro-genital passages. The kidney is especially responsive to cantharidin, and nephritis is a common aftermath of the use of this drug. The glomeruli are the first to respond to its action, though changes take place over the entire nephridium. Cantharidin, taken by the mouth, is quickly absorbed. It has enjoyed a questionable reputation as an aphrodisiac, and too common poisoning occurs from its misuse for this purpose. Its application to the skin as an irritant has to be guarded in practice, lest sufficient of the poison be absorbed to produce acute nephritis and other toxic reactions.

The active principle of the American poison oak, or poison ivy, toxicodendrol, is even more highly irritant than cantharidin. In this case as little as 0.0001 of a milligram is sufficient to produce vesication of the skin. This plant is widely distributed and acute intoxication from it is only too common. In more susceptible individuals toxicodendrol poisoning becomes quite a serious menace to general health. This irritant is soluble in alkalies and in alcohol, but is precipitated by lead acetate. After being exposed to its action, the prophylactic treatment should be to bathe the exposed part in alcohol in order to dissolve the adherent toxicodendrol and follow by an alcoholic solution of lead acetate or other precipitant to remove the poison before its action has proceeded far.

CHAPTER XXXV.

THE VEGETABLE CATHARTICS. IRRITANTS AFFECTING THE ALIMENTARY CANAL.

I.

Introduction.

The substances of the vegetable cathartic group, like the skin irritants, are numerous. A large number of these substances are glucosides which, when the carbohydrate is split off, leave a highly irritant residue. They are usually divided into three great groups: 1. The resinous glucosides, represented by the jalap group; 2. Vegetable cathartics of the anthracene group; 3. Neutral oils which, upon digestion, set free an irritant fraction.

The important representatives of the jalap group are: Jalap, Colocynthin, Podophyllum, Elaterium. The resin from jalap contains the irritant glucoside, *convolvulin*. Colocynthin contains in its fruit the glucoside, *colocynthin*. *Podophyllin* is a glucoside which has been isolated from the may-apple root. *Elaterium* is a neutral substance, the most toxic member of the series. It is derived from the fruit of the *Ecballium elaterium*, or squirting cucumber.

Typical members of the anthracene group are, *aloes*, *senna*, and *rhubarb*. These plants yield irritant substances of which the anthracene nucleus forms the base.

The cathartic oils are two, namely, croton oil, which, upon digestion, sets free the highly irritant *crotonolic acid*, and castor oil, which splits off *risinolic acid*. These cleavages take place during the digestion of the oil.

II.

Outline of Pharmacological Action.

1. *The acceleration of the peristaltic contractions, both of the small and large intestines.*
2. *Stimulation of the secretion of fluid by the mucous lining and by the glands of the alimentary tract.*
3. *The production of local inflammation, which may become drastic when the drugs are used in more concentrated form.*

III.

Details of Pharmacological Action.

1. The nature of the reaction by which the vegetable purgatives produce irritation and catharsis in the alimentary canal.—The recognition of the fact of the irritative action of the group called vegetable purgatives gives us a key for the explanation of their purgative action. The different members of this group induce varying degrees of irritation, and in different portions of the mucous membrane of the canal. As a result of this irritation there is disturbance, not only in the local area of the mucosa in contact with the drug, but, through the complicated nervous relations, marked changes in the reaction of the nerves controlling alimentary motor behavior and secretory processes. For the explanation, therefore, of the complex of catharsis induced by this series, one must hold in mind the entire physiological mechanism involved. This mechanism is described later in connection with the topic Saline Cathartics. At that point some emphasis is laid on the fact that the physiological movements of the stomach and of the intestinal tract are peristaltic in nature. Also that the large intestine is less vigorously active than the small intestine.

Different physiologists, notably Langley, have laid emphasis on the presence and function of the local nervous mechanism, the enteric nervous system. While the question has not been settled beyond doubt, the present indications are that the muscular walls of the alimentary tract execute their peristaltic actions under the influence and control of the peripheral nervous mechanism. At the same time the connections with the central nervous system supply the tract with general controlling nerve complexes, both motor and sensory.

The various diverticula of the mucosa, which have become differentiated into the glands of the alimentary canal, are also brought into coördination with the muscular elements of the canal through regulating nervous mechanisms. With these anatomical and physiological relations in mind, we may venture to discuss the action of the drugs acting through irritation of the mucosa under the following points:

2. Irritant action at the point of contact.—There is a great variation in the intensity of the reactions of the alimentary canal to different members of the vegetable cathartic group. This is partly due to the nature and time of contact as between the drug and the mucosa, and in part due to the toxic character of the drug. From

the interaction of these two factors one may explain many of the physiological phenomena produced by members of this series. In making a comparison of the reactions one must constantly keep in mind that he is dealing with a water moist mucosa, a membrane that is very sensitive to contact environment, and a surface in which the time of contact with the cathartic drug is under the influence of the peristaltic contractions. In the very nature of the case only the early stages of the typical inflammatory processes are ordinarily induced. Emphasis has already been given to the fact that the initial irritative process is stimulative to the sensory nerve endings of the mucosa. The reaction to stimulation in the alimentary mucosa is a reflex change in motor activity, typically the induction of a strong increase in peristalsis. Hence, before an extreme inflammation is induced the increased motility will have driven the irritative agent forward, i.e., away from the point of contact before additional absorption and further irritation has time to occur. This is particularly true of the small intestine. The large intestine, which under ordinary circumstances is stimulated to more vigorous peristalsis and final emptying by reflexes occurring at the bend in the rectum, is in many instances caught up in this general local irritative reaction. Not all members of the series produce equally intense reactions at different lengths of the alimentary tract, and the less irritative members, as a rule, react less vigorously on the large intestine.

However, accelerated peristalsis will not account for all the phenomena observed. Many cathartics produce a great increase in the volume of the intestinal fluids, an effect which has been tested out experimentally on the isolated loops of the intestine. The increased fluid, under usual conditions, is not a transudate, since it is not characterized by the presence of albumin. On the other hand, it is held to be a secretion because the fluid contains digestive ferments.

The vegetable purgatives, therefore, in the milder reactions produce their local cathartic effect by three processes: (1) Increased secretion at the point of contact due to the mild local inflammation. (2) Stimulation to increased peristalsis, through local reflex mechanisms, as well as through general nervous reflexes. And (3) reflex stimulation to secretion through the nervous control of the larger glands connected with the alimentary tract.

The more irritant purgatives are extremely toxic; for example, elaterium. A very small quantity of this drug induces a violent inflammation of the intestinal mucosa, which is shown by congestion

and destruction of the mucous membrane. Such a process leads to the more violent reflexes through the central nervous system, which at first are characterized by increased secretory and circulatory changes. When the contact is prolonged the systemic reactions may become so profound as to border on collapse.

The cholagogue action of many of these drugs is explained by the calling forth of vigorous nerve reflexes, which produce contractions of the gall bladder, rather than by any particular influence they may have on the secretion of bile itself.

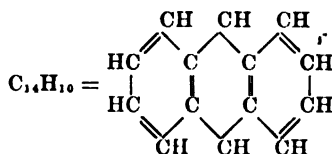
3. Irritant action of the vegetable cathartics after absorption.—The majority of the vegetable cathartics are relatively insoluble; in fact, quite insoluble in the acid gastric juice. Their solubility is promoted by the alkaline secretions, which they meet in the duodenum. They are, therefore, absorbed slowly and reach the circulation in highly diluted form. That they are toxic after absorption, however, is proven by the fact that they tend to induce inflammation in the kidney and in the uro-genital system. Even the mild aloes is sometimes followed by renal ulceration. The more vigorous members are prone to produce inflammation, not only of the kidney, but of other organs of the body not so intimately related to the elimination of the drugs from the system. It is for this reason that the large majority of the vegetable purgatives are contraindicated under certain conditions, as in the case of gastric and intestinal inflammation, nephritis, etc.

4. Purgative action of the anthracene group.—The chief and best known members of this group of vegetable purgatives are senna, rhubarb, cascara, frangula, and aloes. Belonging to the same group in general chemical relation is the mild purgative phthaleins, especially in favor since the work of Abel and Rowntree.¹ These authors studied the cathartic action of a number of phthaleins, showing that phenolphthalein, and more particularly phenoltetrachlorophthalein, are mild and relatively non-irritant cathartics after hypodermic injection.

The materials obtained from the anthracene group of vegetable purgatives have not been purified and isolated. They are used in the form of infusions, extracts, and syrups, made from preparations of the leaves and other parts of the plant. The group owes its purga-

¹ Abel, John J., and Rowntree, L. G.: "On the Pharmacological Action of Some Phthaleins and their Derivatives, with Especial Reference to their Behavior as Purgatives. I.," *Journal of Pharmacology and Experimental Therapeutics*, Vol. I., p. 231, 1909.

tive action to the substances which are apparently derivatives of the irritant anthracene nucleus:



Attempts to isolate pure principles have proven only partially successful. As a group, the preparations are absorbed with difficulty, but when mixed with certain alkalies, for example, bile, they are more efficient. They act, therefore, largely on the intestine, chiefly the large intestine, where they are liable to produce considerable pain and tenesmus.

a. Senna.—Preparations of senna are derived from the leaves of different species of cassia. Two cc., a half-gram, of the fluid extract or the equivalent dose of the syrup, the confection, or syrup of sarsaparilla, is usually adequate to produce cathartic action after six or eight hours.

b. Rhubarb.—The preparations of rhubarb are derived from the root of *Rheum officinale*. The usual dose is 1 cc. of the fluid extract or four times as much of the tincture. Preparations of rhubarb were thought to be especially active in promoting the secretion of bile. This, however, is open to question. The facts are that the outpour of bile aids in the solution of rhubarb and facilitates its action by putting it into more intimate contact with the mucous membrane of the intestinal tract. The presence of a certain amount of tannic acid gives to rhubarb an astringency which is antagonistic to its irritant action.

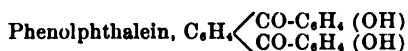
c. Cascara is derived from the bark of *Rhamnus purshiana*. The action of the different preparations of this cathartic are mild and somewhat persistent. Cascara is unusually bitter, a property which is counteracted in practical uses by adding magnesium, licorice or some flavoring substance.

d. Frangula is derived from the laxative bark of the alder-buckthorn, *Rhamnus frangula*.

e. Aloe is a somewhat more vigorous purgative derived from the juices of different species of aloe. It is given in doses of from three to five grains, and is characterized by the rather vigorous griping contractions which it induces in the large intestine and in the rectum.

It enters into a large number of the compound purgative mixtures of vegetable origin.

f. Phenolphthalein.—In recent years it has been shown that the different phthaleins have a mild laxative action on the alimentary tract. For example,



produces this effect in doses of .1 to .15 grms. The phthaleins are not very soluble. Abel and Rowntree especially investigated derivatives of phthalein, in particular phenoltetrachlorophthalein, which they consider favorable for human use as a hypodermic laxative. The most favorable members of the vegetable laxative series do not lend themselves to hypodermic injection, because of the local irritant action and inflammation which they induce. The phthalein compounds are particularly free from this action, inducing their favorable reaction in the body through a stimulative rather than a strictly irritative process. Phenoltetrachlorophthalein is comparatively insoluble in water, but is readily soluble in neutral oils. The authorities quoted used olive oil at a temperature of 210°C. in making their solutions. They gave hypodermic doses of .4 of a gram in 20 cc. of the oil. Catharsis did not occur until twenty hours or more, and continued in mild form for five or six days after administration.

The phthaleins are soluble in the alkaline bile and are excreted from the liver through the bile. In a "normal" case this brings the phthaleins into contact with the intestinal mucosa. In the mildly alkaline content of the large intestine some reabsorption takes place and later re-excretion through the liver, which, according to Abel and Rowntree, is a specific excretory organ for these compounds. It is probable that the cycle of excretion and absorption is the reason for the prolonged laxative action of the members of the phthalein group. Excretion takes place with the feces and, therefore, final elimination is assured.

5. **Purgative action of the members of the jalap group.**—The representative members of this series are jalap, colocynthin, podophyllin, and elaterium. The activity of this group is primarily due to the presence of irritant resins and glucosides. Here too the active principles have been only partially isolated. In comparison with the anthracene series this group is particularly irritant and toxic. One might raise a question as to the classification of the former group with the irritants, but not so in this group. Of all the members the

most toxic is the squirting cucumber, *Ecballium elaterium*, which yields the active substance, *elaterium*.

a. Resin of jalap.—1 to .2 gram of jalap induce defecation in from two to three hours. Larger doses are highly irritant to the stomach and to the intestine. Jalap induces a marked secretion of fluid into the canal, which leads to the production of rice-water stools. The gastric irritation produces nausea and sometimes vomiting.

b. Colocynth.—The extract of colocynth is a purgative in doses of .03 to .05 gram. Its action is accompanied by intense griping, and in larger doses with bloody effusions. Brieger found that a small quantity of colocynth induced hyperemia and increased peristalsis in the isolated intestinal loop. The bloody effusions occasionally noted are due to acute inflammatory processes in the mucosa, which extend to the disintegrative stage and which involve the capillaries.

c. Podophyllin.—In doses of from .4 to .6 gram podophyllin induces purgation in from six to ten hours. In doses of from 1.5 to 2 grams there is nausea with mental depression, pain, and colic. The irritant action is prolonged with this resin, but it is somewhat reduced or counteracted by hyoscin.

d. Elaterium.—This is given in doses of from 1 to 3 milligrams, which induce purgation in two hours. This is the most drastic of all these purgatives. Stronger doses not only produce intense pain, but lead to severe inflammation, mucosal desquamation, and even collapse.

6. The specific action of the neutral oil series.—The purgative oils of this series are castor oil and croton oil. Castor oil is an oil obtained from the seeds of the castor bean, *Ricinus communis*, by compression. The oil itself is not irritant, but when digested the ricinoleic acid is strongly irritant. Croton oil is obtained from the croton bean, *Crotontiglium*. Its methyl-crotonolic acid when set free is peculiarly toxic and irritant. The presence of minute traces of methyl-crotonolic acid in the usual commercial grade of this oil accounts for its irritant action on the skin and mucous membrane before its digestion takes place.

a. Castor oil.—Doses as large as one-half to two ounces of castor oil are used to produce catharsis. This bland oil passes the gastric cavity with little change. It is true, it sometimes induces nausea and vomiting, but not from the specific action of the oil other than its disagreeable taste, especially when not perfectly fresh. In the intestines, however, fatty digestion takes place, setting free the irritant ricinoleic acid. This induces a mild inflammation, which, in this particular instance, does not pass much beyond the limit of a general effusion. The

effect is vigorous enough, however, to produce variation of the peristaltic movements with some reflex stimulation of the secretive mechanism, a result comparable to the mild resinous purgatives. Ricinoleic acid is generally regarded as only slightly more irritative and stimulative to the alimentary tract than the acids from the ordinary neutral oils; for example, oleic acid.

From this classification it is plain that castor oil has considerable value as a nutritive oil, as has the mild olive oil. In certain parts of the Orient,—for example, China,—castor oil is a general article of food.

b. Croton oil.—Upon intestinal digestion croton oil yields the highly irritant and toxic *crotonoleic acid*. A dose of croton oil is given by Hatcher and Sollmann as from 0.01 to 0.15 cc. (1-6 to 2 drops). There is usually enough free acid in the preparation to produce local irritation of the external skin; therefore, to readily produce this change in the mouth and stomach. But when the lipases of the intestinal tract are met, additional neutral oil is dissociated and a more pronounced irritant action ensues. It is said that a single drop of the oil is sufficient to produce stools in from one to two hours, and the inflammatory action with its associated reflexes continues until as many as ten or fifteen stools result. In the case of croton oil the primary action is that of irritation and inflammation. A process that is most vigorous in the duodenal and lower intestinal mucosa. It is from such violent irritants as methyl-crotonoleic acid that most extensive lesion of the canal becomes possible. As little as twenty drops is recorded as having produced death.

CHAPTER XXXVI.

COUNTER IRRITANTS AND THE PHENOMENON OF COUNTER IRRITATION.

All agencies that induce local irritations have, beside a specific effect in the local region, reactions, which affect the coördinative mechanisms of the body. Such effects have long been known in practical medicine, and belong to the category of referred pain, counter irritations, etc.

1. **The theory of counter irritation.**—The fundamental effect is that observed clinically when an inflammatory process of a given portion of the body, the skin, for example, induces favorable changes in diseased conditions of other and distant organs, in this illustration deep-seated organs, as the stomach, the lungs, etc. This knowledge has been, and to a considerable extent still is, largely empirical. Brunton¹ has summarized the facts showing the relation between specific local areas of the skin and particular visceral organs. One of his diagrams we use in Figure 65. The most satisfactory scientific explanation of these remote effects, an explanation that has received quite general acceptance, has been formulated by Head.² Head observed that the pain and areas of tenderness in deep-seated organs during visceral disease were associated with areas of tenderness in the local areas of the skin of the patient. In short, the skin tenderness is an associated condition developed in connection with the diseased condition in the deeper organs. Briefly stated, his view is based on the segmental conception of the structure of the nervous system, viz., that the innervation of the different portions of the body is by nerves derived from segments of the brain and spinal cord. These nerves of each segment are subdivided into somatic and splanchnic branches. The somatic branches are superficial in their distribution, including the skin, muscles, etc., and the splanchnic are deep, including the various visceral organs. Both the sensory and the motor fibers of each typical segment participate in the superficial and deep distribution.

¹ Brunton, T. L.: *Lectures on the Action of Medicines*. New York, 1899.

² Head, Henry: *Brain*, Vol. XVI., p. 1, 1893.

From the standpoint of counter irritation, the sensory nerves, the vasomotors, and probably the trophic nerves are of greatest importance. That these groups of nerves are in close physiological, as well as anatomical, relation to each other as regards their centers in the spinal cord, can no longer be doubted, although the explanation of particular cases has not always been perfectly free of question. In

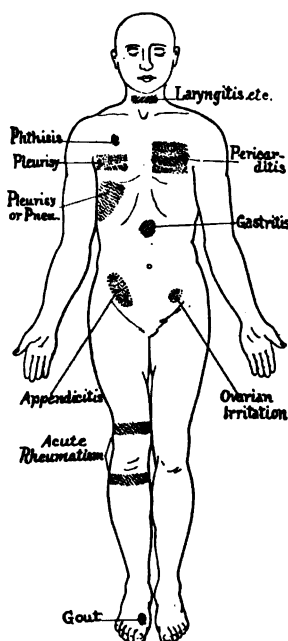


FIG. 65.—Cutaneous areas which are ordinarily used in the application of counter irritants for the relief of inflammation of the deeper organs in the diseases indicated. From Brunton.

Head's words, "Thus to sum up, I think we may conclude that the central connections of the pain fibers from the skin and viscera are closely connected with one another. The central connections of the nerves for heat and cold, and for trophic disturbances in the skin, must also be in somewhat close association, though probably not actually connected." According to the views of Head, and later of McKenzie, it is assumed that the cutaneous sensory nerves from a given segment, for example, from a typical skin area of the trunk region, are in close and intimate relation with the visceral nerves of that particular segment of the spinal cord, or, according to McKenzie, with closely adjacent segments. This relation is so intimate on the

sensory side of the nervous complex that a sensory stimulation occurring in the viscus may be referred to an origin in the more highly innervated skin, or under certain circumstances *vice versa*. This is presumably because the collateral connections, either in the basal segment of the cord or at some higher level in the path, permit the nervous overflow of afferent impulse into a common area of perceiving cortex. Ordinary tactile, and for the most part temperature sensations are absent from visceral organs. The visceral sensory or afferent impulses are chiefly those of the reflex and automatic type not associated with very definite states of consciousness. Visceral pain and the sensations of "fullness" characteristic of hollow organs (Hertz) are the chief visceral sensations. Perhaps appetite and hunger should be considered of this class. These sensations are not very definitely localized. It is for this reason that the symptoms noted in connection with excessive visceral stimulation, or sensitiveness from inflammation, are readily interpreted as an apparently greater irritability of the corresponding cutaneous sensory areas associated with the same spinal segment. There is in fact an increase in the sensitiveness of the segmental centers, such that the usual cutaneous stimulus produces a greater response. Centrally the effect is the same as if the increase had come either from a stronger peripheral stimulus, or from a more sensitive cutaneous end organ.

Cutaneous stimulation that results in vascular reflex dilations in the skin area will at the same time produce a similar degree of vascular change in the deep-seated organ whose coördinating vascular nerves are through the same spinal segment. That is, a light cutaneous stimulus, which is accompanied by a reflexly increased vasomotor tone, i.e., vasoconstriction, will normally produce definite vasoconstrictions, not only in the skin segment, in which the stimulus arises, but in the corresponding visceral region. In certain particular regions there is a primary antagonistic reaction in these correlated areas.

It is observed that a pathological condition, for example an inflammation, of a deep-seated organ may have its blood-supply profoundly influenced by stimulative, i.e., irritative, processes occurring in the corresponding skin segment, and *vice versa*. Vasodilations favor and constrictions retard the reparative cycle. This is the underlying physiological principle justifying the application of skin irritants, such as artificial heat, poultices, mustard plasters, fly blisters, etc., for purposes of counter irritation. By the above hypothesis, the whole explanation of the phenomenon of counter irritation rests upon the anatomical and physiological close association in the cord

and brain-stem of the mechanisms of the automatic and autonomic reflexes coördinating the great nutritive areas of the body. In practical therapeutics the whole process falls back upon the relation of the condition of anemia and hyperemia to metabolism, healing, etc., as suggested above.

A question might be raised here in the application of Head's explanation in the consideration of the disease known as Herpes zoster. The cause of herpes, according to Head, has been ascribed to disease of the posterior root ganglia, i.e., inflammation and hypersensitiveness of the sensory paths. There is, therefore, an interference with the reflexes arising from stimuli occurring in the areas to which the sensory fibers are distributed. It is definitely stated by Head¹: "There is no evidence that deep organs receiving their visceral supply from affected roots become affected during the outburst of zoster." On the theory of associated innervation it would seem that we have a right to expect an inflammatory process, not only in the skin, which does occur, but also in the corresponding visceral segment, which apparently does not occur in zoster. If the deep visceral reflex were looked for in a region containing antagonistic vascular associations, then the visceral region would display not hyperemia, but anemia, and Head's result would be expected. However, the inflammation of the ganglion interrupts the normal reflexes, therefore the closely coördinating center or centers in the cord will not receive the extensive stimulation which characterizes the usual and uncomplicated process of counter irritation.

Irritant drugs or other agents produce the changes associated in counter irritation when acting through some considerable period of time, and with a certain favorable degree of intensity. This is one of the distinguishing factors between a stimulus and a so-called "irritation." If the irritating agent be a drug, for example, a liniment, it produces its effect by direct contact with and absorption into the living tissue. Under ordinary conditions this contact is only eliminated by the slower vascular reactions of the body, which remove or isolate the agent, a process illustrated by the reactions to bacteria and to toxins.

A large portion of the good influences of a counter irritant undoubtedly comes from the reflex influences on the circulation. This is shown by the fact that a cutaneous irritant produces a rise of general blood-pressure, a rise that is attributed not to the changes in the blood-vessels of the skin areas alone, but to general vascular con-

¹ Head, Henry: *Albutt's System of Medicine*, Vol. VIII., p. 630.

3. **Factors in the practical application of counter irritants.**—Most text-books on therapeutics give directions for the practical use of counter irritants, and include precautions to be observed in the adaptation to different physiological conditions that may be met where such agencies are called for. A reference to Figures 66 and 67 will at once show the segmental nerve distributions to the skin, which must be kept in mind in the practical use of counter irritants for the relief of congestion in the thoracic or visceral organs.

4. **List of counter irritant agents.**—From the discussion of the nature of counter irritants it is observed that the number of drugs or other agents which will induce the pharmacological change is large. Some of these agents are mechanical, but most of them are chemical.

Of the mechanical agents *heat* and *cold* lead the list. Both heat and cold are capable of application in such a way as to cover a wide range of intensity of action, and the facilities by which they may be applied to different parts of the body in these days of special mechanisms, particularly of the electrical class, make them the most valuable of counter irritants. *Cold* controlled by the ice bag is valuable in two great ways: first, in controlling the vascular reactions, and second, in depressing metabolism not only of the tissue, which is being acted on by the direct irritant, but, in those cases where there is a bacterial invasion, control of the injurious bacteria themselves.

Drugs which produce irritation of any kind may be relied upon in the same moment to produce counter irritation, especially when the primary irritant is applied to the skin. Irritant processes in the visceral mucosa are not to be neglected in this regard, since they may lead to irritant processes in the somatic region.

The counter irritant drugs range in intensity of action all the way from the mild processes induced by the saline baths to the violent referred reactions set up by the more vigorous caustics. For the discussion of the action of individual members of this series, the reader is referred to members of the group, Skin Irritants, which are the drugs most in favor for the production of counter irritation.

PART II

INORGANIC DRUGS.

K. *Drugs Characterized to Greater or Less Extent by Salt Action.*

CHAPTER XXXVII.

UNDERLYING PRINCIPLES OF SALT ACTION.

I.

General Considerations of the Physical and Chemical Characteristics of Salts in Solution.

1. **Crystalloids and Colloids.**—Physiology has, to a great extent, familiarized us with the different behaviors of the great variety of substances which we introduce into the body as foods. We have learned that the different classes of foodstuffs are in reality representatives of the great classes of chemicals. The proteins, fats, carbohydrates, etc., i.e., the organic foodstuffs, undergo elaborate processes of digestion before they can enter the tissues, while the substances of simpler composition, such as the salts of sodium, potassium, calcium, etc., pass from the alimentary canal into the tissues and reach the circulation with little or no change. In a word, the inorganic salts, as soon as they enter the state of solution, can by relatively simple processes pass through the lining tissues of the alimentary tract, as well as through the walls of the blood-vessels, and thus quickly distribute themselves throughout the body.

When these great classes of materials are examined more critically the striking characteristic is the fact that the salts pass readily into solution, while the organic substances are dissolved with difficulty or, it may be, not at all. These are differences which rest on a physical basis and are expressed by the terms which designate the classes, namely, *crystalloids* and *colloids*, a classification which was made by Graham a half century ago (1861). Graham called the bodies which passed through a membrane crystalloids because they were found to be such substances as the salts of sodium, potassium, lithium, etc., which exist in the crystalline form. Those substances which do not diffuse through a membrane were designated as colloids.

2. **Colloids.**—This class is characterized by the relatively large size of the molecules, also by the fact that they behave in a characteristic way when in solution or suspension. The colloids are of special interest in pharmacology for the reason that they enter so largely into the composition of the tissues. They influence the behavior of these tissues, not only by virtue of their chemical nature, but also on account of their purely physical characteristics. The presence of the colloid markedly influences the movements and relations of the molecules and ions of the salines, i.e., the crystalloids.

3. **Crystalloids.**—Crystalloids are distinguished from the colloids by the fact that they go into solution far more readily. They for the most part pass through animal membranes with comparative ease, and in a general way are far more labile than are the colloids. The size of the molecules in the crystalloids is relatively small, many times smaller on an average than in the colloids.

4. **Dissociation.**—When the molecules of a crystalloid pass into solution they undergo dissociation, whereby the atoms or groups of atoms are separated, carrying electric charges. For example, when sodium chloride is dissolved the molecules of the salt break down or dissociate into electrically charged ions. The sodium ion carries a positive charge, and is called the *cation*. The chlorine ion carries a negative charge, and is called the *anion*. This process of dissociation, or ionization, occurs in practically all inorganic salts. Dissociation, however, does not necessarily break the molecule into simple atoms electrically charged. Many of the anions and cations consist of groups of atoms as in sodium nitrate, NaNO_3 , which dissociates

into positive sodium ions, $\bar{\text{Na}}$, and negative nitrate ions, $\bar{\text{NO}}_3$. Such substances as caustic potash, KOH , dissociate into $\overset{+}{\text{K}}$ and $\bar{\text{OH}}$ ions, the acids as hydrochloric acid, HCl , into $\overset{+}{\text{H}}$ and $\bar{\text{Cl}}$ ions.

5. **Electrolytes.**—Solutions of crystalloids are conductors of electrical currents, hence called electrolytes. This is dependent upon the state of ionization; in fact, the conducting power of a given solution is proportional to the content of ions. The cations carry positive electricity, and migrate toward the negative pole when a current is flowing through the solution. The anions migrate in the opposite direction. The conducting power of a solution varies with the different chemical substances in solution, depending not only upon the number of ions, but upon other diffusion constants. Certain ions,

for example, migrate through a solution with much greater speed than others.

6. Freezing point depression.—The factor of dissociation is shown by the influence which the molecules and ions have on the depression of the freezing point of a solution. In this instance both the molecules and the ions act as individual particles in influencing the freezing point. It is found by experiment that the freezing point depression is directly proportional to the sum of the molecules and ions in solution. When this factor is measured in terms of known constants it is evident that the freezing point gives a direct measure of the dissociation percentage in any given solution. Sodium chloride, 0.9 per cent., which is isotonic for animal tissue, is found to lower the freezing point by 0.56°C . (Hamburger), i.e., the pressure equivalent of 6.5 atmospheres.

7. Osmotic pressure and osmosis.—When chemical substances go into aqueous solution there begins at once the process of distribution of the molecules, also the ions if the chemical be dissociable, throughout the volume of the solvent. The particles of the salt distribute themselves through the solvent according to certain laws. If a certain volume of gas be turned loose at the gas jet in a room, then the laws of gaseous diffusion come into play, and, other things being constant, the molecules of gas will distribute themselves equally throughout the space of the room. Just so is it with a salt dissolving in a beaker of water. The particles of the salt begin to diffuse from their initial location until equilibrium is established. It will then be found that the salt has distributed itself so that each cubic centimeter of the solvent contains the same quantity or number of molecules of the salt. When non-reacting salts are dropped into the solvent at the same time each salt dissolves and diffuses according to its own volume and properties. Each is independent of the other just as in the case of the diffusion of two or more gases in a mixture.

In gases this phenomenon is explained by the fact that each molecule of gas is in free motion with reference to all other molecules in the mixture. Just so is it with the molecules of a salt. Each molecule and ion is in motion and the motion is not hindered by the solvent, hence the ultimate uniform distribution through the solution.

8. Osmosis.—In animals and plants the tissues are separated from each other by surface membranes, though in many animal tissues this surface membrane is not well marked. Such membranes impede the

diffusion of dissolved molecules. Dead membranes prepared for experimentation are found to differ sharply in character. Some will allow the free passage of water, but prevent the passage of dissolved substances. These are called *non-permeable* membranes. Others will allow the passage of certain molecules of dissolved substance and will hinder the passage of others. These are called *semi-permeable* membranes. If the molecules of the salt as well as the solvent pass freely through the membrane, then it is designated as a *permeable* membrane.

Osmotic pressure is shown by instruments which permit the passage of water but prevent the passage of salt molecules. In such an apparatus, where the membrane separates pure water from a solution of a salt in water it can be shown that the water will diffuse into the salt solution as against an ever increasing pressure. When such a diffusion has reached a state of equilibrium the pressure of the salt solution will have increased an amount which is in direct proportion to the increase in number of molecules and ions per unit volume. This passage of water through such a membrane is called *osmosis*. The pressure which it induces in an osmotic apparatus is called *osmotic pressure*.

If the membrane is semi-permeable, then the relations are somewhat different. In this case, if one places on one side of the membrane a mixture of salts in solution some of which can penetrate the membrane and some not, and on the opposite side of the membrane distilled water, then immediately water begins to pass through the membrane into the salt solution, while the permeable salts will begin to diffuse through the membrane into the distilled water. The non-permeable salts are, of course, retained on the original salt side. In this case the passage of the permeable salts by so much reduces the osmotic pressure of the salt solution. Since the rate of diffusion of the salts will vary in each individual case, the osmotic pressure will be represented by a certain curve, which at first rises, because of the more rapid diffusion of the water through the membrane, then more slowly falls as the diffusible salts pass through and distribute themselves throughout the liquid on the water side of the membrane. When equilibrium is established the osmotic pressure on the saline side of the membrane will be represented by the pressure of the non-diffusible salts only, the diffusible salt being equally distributed on both sides.

In permeable membranes a transient osmotic pressure may manifest itself on one side of the membrane as compared with the other,

because of the different rates of diffusion of the different components of the mixture.

The reader will need to consult works on physical chemistry for the mechanism of this process. It is of interest to pharmacologists because osmotic pressures play such an important part in the behavior of living tissues in relation to numerous drugs as well as to salt solutions.

The influence in the body of saline solutions exerted by virtue of their osmotic, electrolytic, and other physical factors is designated by the general term *salt action*.

The protoplasm of the tissues in the animal body does not form quite the same type of surface membrane as is found in the dead osmotic membranes. Nor, in fact, do we find such typical membranes as are present often in the botanical tissues. However, osmosis and isotonicity are always operative factors in the animal body. The protoplasm contains colloidal material, and often this material is condensed into a relatively efficient surface membrane over the animal cell, as in the case of the red blood corpuscles. When salt solutions come into contact with the tissues a process of diffusion as between the solution and the tissues immediately takes place. It will continue until a degree of equilibrium has been established. Unprotected animal tissues will rapidly absorb distilled water by virtue of the osmotic pressure due to the protoplasmic saline content. In like manner they will lose water to solutions of greater concentration, as is shown when red blood corpuscles crenate in hypertonic salines.

The colloids, as differentiated in the tissues, vary greatly in their permeability to different salines. Certain solutions, as ammonium chloride, penetrate practically all tissues with great facility, acting essentially as so much distilled water. Under its influence the blood corpuscles will swell to the point of bursting, and muscle and other tissues undergo a similar increase in volume. Other salts, as sodium chloride in the case of the red blood corpuscles, or the sulphates in the alimentary canal, do not readily pass through the surface of the tissues, and to that extent control the water content of the tissue. A solution of non-permeable salt will lose water to, draw water from, or maintain an equilibrium as regards the water content of a tissue, according as it is *hypotonic*, *hypertonic*, or *isotonic* with the tissue.

It is obvious that salt action plays a very important part in maintaining a proper water content of the tissues of the body.

In other words, salt action is in a very large degree responsible for maintaining an efficient dilution of the chemical components of living substance, under which the protoplasm carries on with the greatest economy its reactions and its corresponding expenditure of energy.

CHAPTER XXXVIII.

WATER.

The introduction of water into the body or the bringing of water into contact with any portion of the body which it wets leads immediately to disturbances of the osmotic balance of the tissues and parts. Of course the skin, which is oily, is relatively impermeable to water, though a certain amount of water is taken up by long contact with the corneous epithelium. The changes induced in the body by the action of water depend chiefly on three factors, namely, the volume of the water, the length of time during which it is kept in contact with a given tissue, and the osmotic permeability of the tissue.

1. **Action of distilled water on isolated tissues.**—When isolated tissue, such as the gastrocnemius muscle or glandular tissue, is immersed in distilled water the cells of the tissue act like osmometers. They imbibe water. The water passes through the surface membrane into the protoplasm as into a colloidal solution. The percentage of water in the tissue, therefore, increases and a condition of hydropic edema supervenes. This water-logging of the tissues interferes with the normal physiological reactions, and if carried too far it leads to degeneration, hence the destruction of the tissues.

A rhythmically contracting strip of cardiac muscle when immersed in distilled water will continue its rhythm for some time, but the relaxation process is interfered with. The rhythm ultimately ceases, therefore, with the muscle in the systolic phase. Skeletal muscle is somewhat similarly influenced. These results are due not only to increase in water content, but to a loss of saline constituents, especially from the interstitial spaces of the muscle.

It is not so easy to determine the exact changes in the functional activity of glandular tissues, but they too absorb water and swell.

Certain living organisms like protozoa, embryos, such as those of the fish, for example, fundulus, and certain special modifications of tissue like the epithelium of the gills of fishes, withstand the action of distilled water with a remarkable degree of resistance, provided

the water contains no toxic impurities to vary the normal resistance of these tissues. It is true that organisms often thrive better in waters derived from natural sources, such as springs and the like, but such waters contain one or more saline constituents, which are the favorable ingredients.

2. Drinking water.—An individual takes large quantities of water as a part of his necessary daily food. This water is brought into contact for some time with the lining membrane of the stomach and intestine, through which it is ultimately absorbed. Water taken by the mouth, therefore, ultimately reaches the blood stream and is distributed throughout the body. Experimental physiology teaches us that very little water is absorbed from the stomach, but that absorption from the intestine is free and rapid. Water enters the body so slowly by this channel that it is very gradually distributed, with the result that it never at any time very sharply raises the percentage of water content of the body fluids and tissues. For example, a glass of water, which contains 250 cc., will be absorbed within 20 to 30 minutes. Since the proportion of blood is approximately one-thirteenth the body weight, the glass of water in a man weighing 130 pounds would be distributed in ten pounds of blood, i.e., about 5000 cc. Since this blood comes into contact with the tissues every 30 seconds, the further distribution of the water obviously would take place so rapidly that the water percentage of the tissues would never be increased from the operation more than a fraction of one per cent. Conditions of extreme thirst are usually associated with diminished water in the tissues, i.e., hypertonicity in the system. Under these conditions the absorption of as much as one or two liters of water would only increase the water content of the tissues by one to three per cent., assuming no elimination during the absorption.

Whether or not the drinking of large quantities of water with our daily meals is injurious has recently been put to test by Dr. Hawk in the University of Illinois laboratories. It would seem that the taking of large quantities of water with meals, i.e., at the beginning or close of the meal, not with the mastication of the foods, is followed by relatively slight or insignificant influences on either the efficiency of the digestive processes or the utilization of the foods in tissue metabolism when tested against the usual and ordinary methods of taking drinking waters.

3. Mineral waters.—Mineral waters should rather be regarded as solutions of certain salts. Therefore, the reactions of the body to these special waters can best be designated under the headings involv-

ing the particular salts contained in the particular waters. The reader is accordingly referred to those sections.

4. The influence of water on metabolism and on the kidney.—

There is one phase of the influence of water on metabolism that should not be lost sight of, namely, the fact that a relatively high water content of the tissues is associated with the period of greatest growth and physiological activity during the life cycle. This statement is particularly true with regard to the growth processes. The tissues of embryos and of the developing young always contain a relatively high percentage of water as compared with the same tissues of adults. As an example of this fact may be quoted the rate of repair in the epidermis of frogs kept at different isotonic levels as regards the salt content of their tissue fluids. Hypotonic frogs repair their tissues much more rapidly than hypertonic frogs.

A hydremic condition is favorable to a greater excretion of water by the kidney. Very excessive ingestion of water, therefore, is rather quickly adjusted by elimination through the excretory organs. In other words, pure water is a sharp and efficient diuretic. The large quantity of urine excreted under this condition eliminates not only water, but the water carries with it both salts and waste organic products. These are present, however, in relatively less condensed form. Under extreme toxic conditions where the absorption of water from the alimentary tract is too slow for efficiency sterile distilled water may be injected directly into the veins, of course in moderate and guarded amounts and preferably in the form of isotonic physiological salines.

CHAPTER XXXIX.

ISOTONIC PHYSIOLOGICAL SOLUTIONS.

Artificial physiological solutions have been in general use now since 1869, when Nasse¹ gave us the basis for our physiological saline. Such solutions primarily attempt to maintain the physical factors of the blood serum and the body fluids. This is accomplished by a mixture of salts in such proportion as to be isotonic with blood serum. Of these solutions the ones in most common use are physiological saline, Ringer's solution, Locke's solution, and other similar solutions with minor variations made to improve the exact physiological balance of the constituents. Artificial physiological solutions are often of extreme practical value in supplying great loss of blood, or in other pathological conditions of one sort or another. They have been of inestimable value in scientific research on living tissues. Physiology teaches us that many of the protoplasmic differentiations in the animal body continue to live and exhibit normal reactions through remarkably long periods when they are bathed in these solutions. If the saline solutions are kept sterile and adequately aerated they are even quite adequate to the growth needs of isolated tissues for a limited time.

1. **Physiological saline.**—That sodium chloride in 0.6 per cent. solution would maintain the striated muscle of a frog in a living active condition for a long period was first shown by Nasse. Similar experiments were applied to other organs and tissues of the body, the first being the cold-blooded heart. Out of this classical beginning has arisen all the present extensive use of artificial solutions for physiological, pathological, and practical medical purposes.

Physiological saline is made up in adaptation to the blood and tissues of each animal according to the isotonicity of its serum. For mammals this isotonicity is represented by a 0.9 per cent. sodium chloride solution. Isolated tissues and organs of the cold-blooded animals, and to an extensive degree of the warm-blooded animals also, remain active and living in physiological saline for several hours. However, physiological saline is not a chemically indifferent solution

¹ Nasse, O.; *Arch. f. d. ges. Physiologie*, 1869, Vol. 2, p. 118.

characterized by physical properties alone, as is too often taught. It fails to support continued tissue activity as would the serum of the animal. The solution is not toxic in the usual sense, but merely fails to supply certain needs of the living tissue. Under its influence isolated hearts at first contract strongly and with good rhythm, but later rapidly lose their amplitude of contraction, though rhythmicity may be retained for a longer time. Skeletal muscle rapidly diminishes in irritability. Cushing has shown that the power of the nerves to transmit a stimulus to the muscle drops out even earlier than the irritability of the muscle to which the nerve may be attached. Such experiments strongly argue against the efficiency of the purely physical factors in all artificial physiological solutions.

The matter may be looked at in another light. Isotonicity obtained by a single salt does not and cannot maintain a physical balance against a body fluid in which the osmotic pressure is due to a complex of salts. Living tissues lose to physiological salines certain necessary ions, and this in itself ultimately disturbs the physical balance in such a way as to change the physiological reactive property of the tissue.

2. **Perfusions of physiological salines.**—Physiological saline is in practice introduced into the body by one of two methods, either by hypodermoclysis or by transfusion directly into a vein. In the former case the saline enters the body relatively slowly, though large amounts may be introduced by the method. In the second case the saline enters the blood stream directly and is under the control of the manipulator. Sterile physiological saline may be transfused without danger for as much as 20 to 30 per cent. of the total normal blood of an animal, one to two liters in the case of man. It is evident that this gives a valuable agent for quickly returning the necessary volume of blood in cases of excessive loss from traumatism, etc. The amount of blood in a normal average adult is from six to eight liters, i.e., one-thirteenth of the body weight. The introduction of two additional liters, even when one-third the normal blood is lost, will give a blood mixture that contains only approximately 30 per cent. physiological saline, and this percentage is very quickly lowered by interdiffusions between the blood and the tissues of the body. Such a dilution of the blood is far less drastic in its effect on the tissues than is generally supposed, less, in fact, than in experiments on isolated organs immersed in a pure physiological saline. The isotonicity factor throughout is maintained at a constant, the sodium chloride content of the plasma is constant, while the other saline constituents

of the plasma and tissues are lowered, yet not so violently disturbed and hence readily regain their balance.

There are numerous experiments that indicate that the sodium chloride, as such, is mildly stimulative to protoplasmic activity. Granting this point, it follows that its addition as physiological saline to the extent of as much as 30 per cent. of the volume of the blood will slightly raise the irritability, i.e., the general activity of the tissues. This, of course, is favorable in the case of excessive shock, excessive bleeding, etc., where the clinical use of physiological saline or other normal physiological solution is called for.

The introduction of relatively large volumes of physiological saline causes slight rise of blood-pressure purely because of the increased volume of blood. This factor is favorable to the eliminative processes, the chief of which is the excretion of fluid through the kidney. Physiological saline is a diuretic, therefore. In driving a large quantity of fluid through the kidney a considerable quantity of the saline constituents of the blood are carried along. The process also favors the elimination of organic waste products, such as urea, etc., and of toxins, drugs, etc., just as happens when there is an increase of the volume of blood by the absorption of drinking water.

3. **Ringer's solution and its modifications.**—In the early eighties Ringer clearly showed that physiological saline was inadequate because it lacked certain necessary salts present in the serum, namely, potassium and calcium salts. From his work we have derived the numerous physiological solutions which bear his name.

A wide variety of percentages of constituents in Ringer's solution has been used, especially in recent times. This is due to the attempt to maintain the actual saline balance which exists in the blood serum of the animals used in the experimentation, the different species varying widely in this regard. Loeb¹ states: "We have a point of attack for the investigation of the rôle of the salts in the fact that the cells of our body live longest in a liquid which contains the three salts, NaCl, KCl, and CaCl₂ in a definite proportion, namely, 100 molecules NaCl, 2.2 molecules KCl, and 1.5 molecules of CaCl₂. This proportion is identical with the proportion in which these salts are contained in sea water; but the concentration of the three salts is not the same in both cases. It is about three times as high in the sea water as in our blood serum." In laboratory practice it is found that for cold-blooded vertebrate and for mammalian tissues the percentage of potassium and calcium is a little higher. The physiological bal-

¹ Loeb, Jacques: *The Mechanistic Conception of Life*, p. 169.

ance was determined for terrapin ventricular tissue by Greene¹ and is represented by the following solution:

0.7	per cent.	sodium chloride
0.03	" "	potassium chloride
0.026	" "	calcium chloride.

Certain laboratories slightly increase the amount of potassium chloride for use with mammalian tissue up to 0.042 per cent., and add a trace of alkaline sodium bicarbonate. The amount of calcium in the above mixture is based on quantitative analytical determinations in sheep serum (Howell) and terrapin serum (Greene).

The Ringer's solution not only maintains total isotonicity as such, but it maintains an isotonicity of the three most important salines of the body fluid. In oxygenated Ringer's solution many of the body tissues behave remarkably like normal tissues.

The inorganic salts in Ringer's solution are not supposed to furnish potential energy, still these salts are essential to the living activities of the body tissues. Quoting again from Loeb: "If we now raise the question as to why salts are necessary for the preservation of the life of the cell, we can point to a number of cases in which this answer seems clear. Each cell may be considered a chemical factory, in which the work can only go on in the proper way if the diffusion of substances through the cell wall is restricted. This diffusion depends on the nature of the surface layer of the cell. Overton and others assume that this layer consists of a continuous membrane of fat or lipoids. This assumption is not compatible with two facts, namely, that water diffuses very rapidly into the cell, and second, that life depends upon an exchange of water-soluble and not of fat-soluble substances between the cells and the surrounding liquid."

A definite nutritive substance was first added to the Ringer's salt solution by Locke.

4. **Locke's solution.**—Locke added 0.1 per cent. of dextrose to Ringer's solution in the attempt to furnish the tissues with a definite oxidizable energy-giving substance. He found that the addition prolonged the life of the tissues beyond that of strictly inorganic Ringer's.

The contention of Locke has been confirmed in more recent times, and it is now definitely known that isolated organs when perfused with Locke's solution can utilize the sugar. For example, Lee and Salant²

¹ Greene, Chas. W.: *American Journal of Physiology*, Vol. II., p. 125, 1899.

² Lee, F. S., and Salant, W.: *American Journal of Physiology*, Vol. VI., p. 61, 1902.

found that if parallel gastrocnemius muscles from the same animal were perfused, one with Ringer's solution and the other with Locke's solution, the latter maintained its contractions for a longer time and recovered from fatigue more readily. One of the best demonstrations of this point has recently been given by Knowlton and Starling,¹ who determined the rate of oxidation of sugars by isolated mammalian hearts, showing that oxidation not only occurs, but it occurs in surprisingly constant proportion per gram of tissue.

In perfusions with Locke's solution one must not lose sight of the fact that well oxygenated fluid must always be used. Body tissues quickly use up the interstitial oxygen and must receive a supply from the outside. When mammalian tissues are perfused with inorganic solutions, i.e., solutions which do not contain the special oxygen-carrying pigment, hemoglobin, it is customary to insure oxygen saturation by bubbling pure oxygen through the artificial solution, or by putting the solution under a positive pressure of pure oxygen.

5. Sera and lymphs as physiological solutions.—In the body the blood plasma or the lymph is the normal fluid for the living tissue. Naturally when artificial solutions are to be used the ideal fluid would be the one in which the tissue has developed. Lymph and serum not only contain the inorganic salts which contribute chiefly to maintain the constant physical factors, but also numerous traces of salts that have been absorbed from the foods or are being excreted after more or less oxidation by the tissues. The organic nutritive substances are also present in the normal body fluids, the proteins and their derivatives, fats, and the various carbohydrates. These are the great classes of organic compounds present. Besides, there are substances always present in the blood and lymph which are developed in response to special conditions which may be impressed upon the organism at some time in its life history. These substances are far from indifferent chemically, if ignorable physically. One has only to refer to the numerous toxins, antitoxins, lysins, etc., which are now of such tremendous bacteriological and hygienic interest. There are also present those materials derived from the reactions of the tissues themselves, i.e., the organ extracts, enzymes, oxidases, waste products, etc.

The serums, therefore, must vary greatly and fundamentally if one takes into consideration their source in different species, and in different individuals even of the same species. Because of this great variation in composition, particularly as regards the subtler

¹ Knowlton, F. P., and Starling, E. H.: *Jour. Phys.*, Vol. XLV., p. 146, 1912.

chemical constituents, it is found that a serum or a lymph derived from one animal may be not only not normal, but even toxic to another animal. The detail of these factors is discussed in text-books on bacteriology, vaccines, sera, organ therapy, etc. Considered from the present point of view, a physiological solution that maintains through the agency of inorganic constituents normal to sera the physical constants will be safer and more nearly inert in those relations where it is desired to maintain the pharmacological or therapeutic isotonicity of tissues or organs.

6. **Summary.**—Physiological saline, 0.9 per cent. sodium chloride for mammals, is a valuable agent for increasing the volume of blood. It maintains physiological isotonicity, and has the minimum of reactive power. It is a diuretic, acting as a mild stimulus to the renal epithelium and favoring the mechanical separation from the blood of the salines and other wastes. It may be introduced into the circulation of a mammal after excessive loss of blood, in man to the amount of one or even two liters. This somewhat lowers the concentration of the other salts of the blood, but not to a level that is injurious under any ordinary condition.

Ringer's solution is more favorable because it is a more normal solution of the salts in the proportions found in blood. An exactly balanced Ringer's solution represents the best transfusing fluid, and should always be used when available. It maintains isotonicity not only of the sodium chloride, but of other salts of the blood. Under its influence the tissues continue their protoplasmic life for a surprisingly long period.

Locke's solution has all the advantages of Ringer's solution with the added advantage of furnishing an energy-giving substance which the living tissues, especially the muscular tissues, can immediately use. The heart and the skeletal muscles can oxidize the sugar from a Ringer's solution.

Lymphs and serum derived from the same species of animal, particularly from the same individual, are more nearly normal to the tissues than the artificial salines. However, species differences in serum, and sometimes individual differences, render the serum toxic. This is particularly true where the individuals have been subjected to disease or experimental treatment, thereby inducing the changes in the serum characteristic of disease. Transfusions of blood, i.e., serum, are much more dangerous on these accounts than are transfusions of balanced saline solutions.

L. Detailed Action of Salts Normal to the Body Fluids and of Their Chemical Relatives.

Any discussion of the specific reactions of the salts normal to the body fluids leads one at once into that complex of salt action which depends on the ionizing properties of these substances. In other words, the reactions of a salt in the body are at least threefold, i.e., the reactions of the salt molecule as such, the reactions of the positive ion, and finally, the reactions of the negative ion. Take, for example, the most abundant salt in the blood plasma, sodium chloride. This salt dissociates to the extent of some 83 per cent., forming positive Na^+ ions and negative Cl^- ions. The undissociated molecules and each of the ions can exert an influence on the living protoplasm. This particular salt is considered the most inactive of any present in the body, yet what action it has depends more largely upon the influence of the ions than upon the undissociated molecules. It is similar with other salts, such as potassium chloride, or the calcium and magnesium phosphates, or of any one of the numerous related inorganic salts. In the case of the potassium or calcium salts, for example the chlorides, it is found that the potassium or calcium cation is far more reactive with the body tissues than the chloride anion.

According to the most recent views the salts react chemically through the formation of ion proteins. Perhaps to some extent molecular proteins are also formed. Such compounds exert their influence on the protoplasm both chemically and physically. The plasma membrane which covers or bounds the animal cell is a controlling agency for the diffusion into or from the cell. Attention has already been called to the influence of the plasma wall on the reactive life of the tissue cell. Variations in the ion protein compounds are responsible for the character of this wall. With these general principles in mind we may take up the detailed discussion of the action of the individual salts.

CHAPTER XL.

THE SODIUM AND POTASSIUM GROUP, INCLUDING CHLORIDES, BROMIDES, IODIDES, SULPHATES, NITRATES, ETC.

I.

The Sodium Salts.

The salts of the alkali metals are of special interest because of the action of their bases. Yet these salts have long been considered as the chief agents for maintaining the physical isotonicity of animal tissues.

1. **Sodium chloride and the sodium salts.**—Sodium chloride is normal to the blood plasma and the various lymphs. It is present in larger proportion in these fluids than any other inorganic constituent. It is assumed that sodium chloride is ionized in the plasma fluids just as it is in the simpler solutions. Its action, therefore, can be attributed to the reactions induced by the positive sodium and by the negative chlorine ions. Sodium chloride in pure solutions increases the permeability of animal tissues. This point has been established in a peculiarly interesting way by R. Lillie.¹ Lillie found that if the larvæ of the sea worm *Arenicola* are placed in sodium chloride solution isotonic with sea water their muscles strongly contract for some seconds, then slowly relax. The cilia of the surface not only cease contraction but undergo rapid disintegration. Lillie explains this result as due to the increase in permeability of the epithelial tissue under the influence of the sodium chloride. In this case the change in permeability is coincident with the stimulative action. In many mammalian tissues, i.e., skeletal muscle, heart, etc., it has been shown that sodium chloride increases the physiological reactions, in other words is stimulative. When this stimulative effect is not prevented by the antagonistic action of other ions it may lead to toxic disintegration. This is the explanation of the so-called toxic influence of pure sodium chloride. It is greater, of course, in the more concentrated solutions. While isotonic sodium chloride solutions are of great benefit in medicine and surgery, the

¹ Lillie, R.: "The Physico-chemical Conditions of Anesthetic Action," *Science*, Vol. XXXVII., p. 959, 1913.

concentrated solutions occasionally used are a positive source of danger. Several accidents are on record of deaths from the erroneous use of concentrated salines as enemas.

2. **The bromides.**—Of all the sodium salts the chlorides are the most indifferent. The bromides are also relatively indifferent, but exert a greater toxic influence than the chlorides. Certain tissues, like the muscular tissues, can be kept in a living condition and relatively normal in reactions with isotonic sodium bromide solution. This solution reacts in very much the same way as physiological saline solution. The bromides exert a strong depressing action on nerve tissues, reducing the sensitiveness of nerve centers to reflex stimulation, therefore acting as sedatives.

3. **The iodides.**—The sodium iodide is still more toxic than the bromide. The toxicity is due chiefly to the iodide anion which is strongly irritative to mucous surfaces. Sodium iodide is relatively less toxic than some of the other iodides, for example the potassium. This is due primarily to the inactivity of the sodium cation.

4. **Sodium nitrate.**—Sodium nitrate is still more toxic from the action of the nitrate ion. This salt readily diffuses through the tissues and sodium in this form is rapidly excreted by the urine. The nitrates are, as a matter of fact, stimulative to the renal epithelium and to that extent are diuretic.

5. **Sodium sulphate.**—Sodium sulphate introduces a new type of anion, since the sulphate ion is relatively non-diffusible. The non-diffusibility of the anion holds back the diffusion of the cation, hence sodium sulphate is not so readily absorbed from the alimentary canal. This salt is, therefore, a saline cathartic and will be discussed more fully under that group. Sodium sulphate is strongly stimulative to certain tissues, particularly muscle, both striated and smooth. Loeb long ago showed that striated muscle in sulphate solutions was stimulated to contractions of a rhythmic character.

6. **Sodium phosphate.**—Sodium phosphate, Na_2HPO_4 , is a non-diffusible salt, due in this case also to the anion. The salt, as a whole, exerts little influence on the body other than that of its salt action.

II.

The Potassium Salts.

Potassium is the second most important of the alkaline metal bases. Potassium salts, especially the chlorides, bromides, etc.,

readily dissociate in the body fluids. In contrast with sodium salts, potassium salts are very active chemically. The potassium cation may readily form ion protein compounds and these compounds are apparently more fixed than in the case of sodium. Potassium possesses less salt action and more chemical action in the body and is therefore relatively more important. Potassium salts react strongly with muscular tissues, also with nerve, gland, etc. Analyses of muscular tissues and of the fixed elements of the blood show a comparatively high percentage of potassium.

The physiological changes induced by potassium depend upon this chemical affinity. The most important of the potassium reactions are those on muscle and on nervous tissues.

Potassium is of tremendous importance in maintaining a favorable physiological condition for the heart. Numerous investigations which have been emphasized in the discussions of physiologically balanced solutions go to show that the character of the normal contractions of the heart is absolutely dependent upon the presence of potassium in the blood and lymph. Potassium reacts here with the heart proteins in some sort of opposition to sodium and calcium. When the potassium content of Ringer's solution is increased, then the heart beats slower, relaxes more completely, and contracts with less amplitude. If the potassium content is further strengthened the heart will cease to beat. Even with the mammalian heart the addition of potassium chloride to a perfusion of Locke's or Ringer's solution is sufficient to bring the contracting heart to a standstill. This standstill is quickly removed by the elimination of the excess of potassium, showing that the condition imposed upon the heart is at least not a strongly fixed chemical combination. This holds true for all forms of vertebrate heart that have been investigated.

The skeletal muscles contain in their ash a considerable quantity of potassium. If the potassium in the lymph and blood circulating through skeletal muscle is increased, then the contractions of the muscle are weakened and the irritability diminished or lost entirely. This point has also been nicely demonstrated by Lillie on the *Arenicola* larvæ referred to above. These larvæ swim normally by two mechanisms; first, by the action of trochophoral cilia, which we have already seen are readily poisoned by the sodium chloride solutions, and second, by the contractions of longitudinal muscles in the body wall. Potassium solutions render the muscles inert without interfering strongly with the action of the cilia. Larvæ poisoned in this

way remain rigid from inactivity of their longitudinal muscles, but swim about freely by ciliary movement.

Undoubtedly potassium is toxic to glandular tissue. This is well shown by the toxicity of potassium solutions on the kidney.

On nerve tissue potassium is a marked depressant. This is borne out by the diminished sensitiveness of the peripheral nerves as well as the depression noted in the reactive power of the central nervous system after large doses of potassium salts. This depression is particularly manifest through diminution in the reflexes. In extreme toxicity the condition may amount to central nervous paralysis.

The potassium bromides are much more depressant than the chlorides, due to the added action of the potassium ion. In this case, since the bromide acts almost specifically on the nervous tissue, it follows that the potassium bromides will have a much more profound sedative effect on the central nervous tissue.

Potassium iodides are still more toxic. The potassium and iodine ions are apparently particularly toxic for the more generalized tissues. This salt is used in therapeutics in combating certain infections, particularly invasions of *spirochæte pallida*.

Other salts of potassium, namely, the nitrates, sulphates, citrates, and phosphates react in the body in a way comparable to the corresponding salts of sodium. The principal difference is in the fact that the depressing factor of the potassium cation is added to each salt. Further discussion of this group will be considered under the heading of saline cathartics.

III.

Ammonium Salts.

Because of similarity of chemical reaction, the ammonium salts will be discussed in connection with salts of sodium and potassium. Ammonium chloride is more diffusible than either sodium or potassium chloride. In fact, in the body the ready diffusibility of this salt prevents it from exerting an osmotic pressure where salts of sodium or potassium would accomplish this result. Ammonium salts are rapidly absorbed and readily diffuse through the body.

1. **The secretions.**—Ammonium chloride especially acts as a vigorous stimulator of the secretions. This is accomplished through the twofold action on the mechanism, i.e., by reflex stimulation and through direct excitation of the secretory nerve center. Ammo-

nium chloride is particularly efficient in stimulating the secretions of the respiratory tract and it is on this basis that it has gained its reputation as an expectorant.

2. **On the nervous system.**—Ammonium salts heighten the irritability of the cord and medulla. This is shown by the increased reflexes and in some cases convulsion-like spasms. The stimulation of the medullary centers shows itself through the various end organs connected therewith. The heart is slowed by vagus inhibition, respiration is accelerated, and the peripheral blood-vessels are constricted, though the reaction is mild in all these cases.

The salts of ammonia have an irritant effect on mucous membranes, leading to excitation of sensory structures found there. These irritations reflexly produce a slowing of the rate of respiration, which is antagonistic to the central effects which come later, a more pronounced cardiac inhibition, and in some cases bronchial contractions. The volatile hydrate of ammonia is particularly irritant to the respiratory tract, a fact which is recognized in the use of ammonias for reviving persons when in a condition of depressed nerve irritability, as for example in fainting, deep anesthesia, etc.

3. **Excretion.**—Ammonium chloride and the fixed salts of ammonia are eliminated as such through the kidney, but the oxidizable forms of ammonia, for example the acetates, citrates, carbonates, etc., are converted in the body ultimately into urea and eliminated as such.

IV.

The Lithium, Rubidium, and Cesium Salts.

These members of the alkaline metal group are of relative insignificance in pharmacology. These bases are not normally present in the body except perhaps in traces. On the other hand, they have in the past received some medicinal emphasis, especially lithium.

Lithium salts do not closely resemble either sodium or potassium in physiological action, but are rather more comparable to calcium. It has long enjoyed a reputation as a saline diuretic. This is due largely to its presence in certain mineral waters of therapeutic value. It was thought, through work in the middle of the last century, that there was a marked reaction as between lithium and uric acid, whereby the latter was increased in solubility in water. A more careful investigation of this problem was made by Good,¹ who,

¹ Good, C. A.: *Am. Jour. Medical Sciences*, February, 1903.

as a result of a number of experiments on mammals, came to the conclusion that lithium is excreted in the saliva, in the stomach and intestine, and in the urine, the greater amount being excreted by the latter. It makes its appearance in the secretions within a few minutes after administration, and may still be detected after 23 days. Lithium salts do not possess any diuretic action other than their salt action, and they are not solvents for uric acid or the urates. The lithium salts possess a degree of toxicity to the general system, as shown by the symptoms of nausea, vomiting, and diarrhea, followed by emaciation, weakness, and even death. These symptoms are in part accounted for by marked enteritis indicating an irritative or corrosive action on the mucous membranes, particularly of the stomach. Good's whole investigation would tend to discredit any favorable therapeutic result to be obtained by salts of this metal.

CHAPTER XLI.

THE SALTS OF THE CALCIUM AND MAGNESIUM GROUP IN COMBINATION WITH VARIOUS ANIONS.

The salts of the alkaline earths play a very important rôle in the physiological economy of the mammalian body. These salts not only constitute the inorganic constituents of the skeleton and other hard parts of the body, but they, particularly calcium, are vitally important constituents of the tissues and body fluids. Both calcium and magnesium are deposited in the bones of the skeleton as well as in epidermal modifications, i.e., the teeth, etc. The adequate supply of calcium and magnesium available in the food of animals is essentially a physiological question. However, attention may be called here to the fact that the amount of these salts called for bears a very close relation to the state of maturity and growth of the animal, as well as the general nutritive factors. Adult animals whose skeletal elements are already fixed require only a very small quantity of calcium and magnesium in comparison with developing young, or with adult females bearing developing young. Deficiency of calcium and magnesium in the food leads to distressing conditions of general metabolism. From a medical point of view these conditions are indicative of malnutrition and are noticed most often in the poorly fed children of the tenement districts of our large cities.

I.

Calcium Salts.

Calcium salts are present, not only in the bones and hard parts of the body, but in all the body fluids and tissues. The ash of the various tissues contains a small portion of calcium. It is not easy to determine in just what form the calcium is present. Probably in many of the tissues and fluids it exists as a calcium phosphate. In blood plasma, lymph, and in some of the secretions, as for example milk, calcium can be precipitated as a free salt. In the main, however, it is assumed that the calcium forms ion proteins in the tissues.

Calcium enters into the reactions of many forms of tissue metabolism. Of these may be mentioned blood-clotting, the coagulation of milk, the rhythmic reactions of muscular tissue, etc. Calcium chloride in the percentage 0.026 is a normal constituent of Ringer's and Locke's solutions. It is present in blood plasma in this particular concentration, as already referred to on page 300. Although calcium probably exists in blood as a phosphate, its reactions have, in the main, been demonstrated through the reactions of calcium chloride in which the chloride ion is relatively inactive.

1. **Calcium in relation to the heart.**—Calcium is a salt necessary for the normal contractions of cardiac muscle, a fact that has been

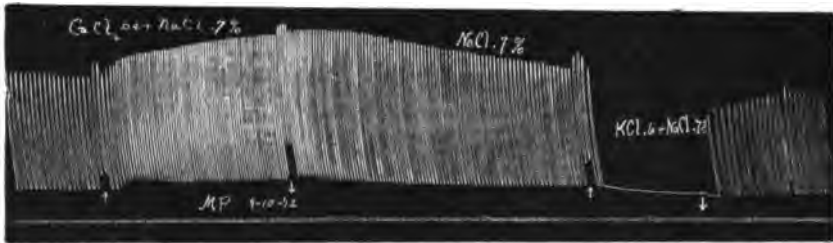


FIG. 68.—Calcium on the rhythm and amplitude of the ventricular strip of the terrapin. The strip was contracting rhythmically in 0.7 per cent. physiological saline. At the point marked by the first arrow it was changed to calcium chloride 0.04 per cent. in sodium chloride 0.7 per cent. The rate increased from 12 to 27 per minute. On returning the muscle to 0.7 per cent. sodium chloride, the amplitude remained higher than normal, though diminishing. A bath of potassium chloride 0.06 per cent. in sodium chloride 0.7 per cent. entirely suppresses the rhythm. However, this quickly returns in normal physiological saline. New tracing by Miss Pile.

established through the work of Ringer, Howell, Loeb, and their numerous students. If the amount of calcium in normal saline solutions be increased and tested on any rhythmic portion of the heart of the cold-blooded vertebrates, or, in fact, the mammal, it will be found that both the rhythm and the amplitude are favored by quantities slightly above the normal of the blood plasma of the animal. Solutions several times more concentrated than the above are always injurious to the tissues, cardiac tissue tending to develop a strong tonic contraction with marked predisposition to fibrillation, and final loss of fundamental rhythm with inability to relax. The latter is a sort of calcium rigor and is removed with some difficulty. Calcium forms an indispensable antagonist for potassium salts (Howell) and sodium salts (Loeb) of the body fluids.

2. **Calcium in the coagulation of blood.**—That calcium was a necessary factor in the coagulation of blood was shown by Schmidt, and has been confirmed by numerous later investigators. If the

calcium is eliminated from the blood plasma the clotting cannot occur until free calcium is again introduced. This is shown in the reactions of oxalate plasma. It is obvious that an increase in the amount of calcium above the normal favors the coagulation of blood. This increase must be slight, however, as an excessive quantity of calcium hinders the reaction, hence becomes toxic.

3. **Nerve tissue.**—Calcium salts favor the normal reactions of nerve tissue. This is demonstrated by the work of Cushing, who showed that the sensitiveness of motor nerve endings that have been depressed by physiological saline is regained by the perfusion of solutions containing calcium in normal amounts.

4. **On metabolism.**—That calcium is a factor in metabolism is suggested by the behavior of cardiac muscle under its influence. Although the matter is not so clearly worked out, it is generally believed that the pathological condition of osteo-malacea is dependent upon interference with calcium in skeletal metabolism. The matter is not a simple lack of calcium, but rather a failure of some factor entering into the general reaction, whereby normal metabolism is deranged.

Calcium is present in blood plasma and takes part in the chemical changes that occur during blood-clotting.) It is also a necessary constituent in the formation of casein from caseinogen. Blood-clotting can be influenced by varying the amount of calcium present in the plasma. When calcium precipitants, like the citrates or the tartrates, are introduced into the alimentary canal in sufficient quantity, or guardedly into the circulation, the elimination of the calcium reduces the coagulability of the blood. The raising of the calcium content to increase coagulability, for example to prevent the post-partum hemorrhage, has also been attempted. In the last instance the clinical possibilities are complicated by the fact that excess of calcium salts does not aid, but retards the process of coagulation, which it is sought to facilitate.

5. **Excretion.**—Calcium salts are poorly absorbed because of the non-permeability of the mucosa of the digestive tube to the calcium cation. Those salts of calcium, like calcium sulphate, which contain a non-diffusing anion, are, of course, absorbed from the alimentary tract with greater difficulty. It follows, therefore, that calcium salts taken by the mouth are excreted largely with the feces, never having been more than slightly absorbed. But calcium is also excreted in small quantities in the urine, and possibly, to some extent, through the mucous membrane of the lower reaches of the alimentary tract.

II.

Magnesium Salts.

Magnesium salts have not been shown to have the intimate relation to normal metabolic processes which characterize the calcium salts. The one exception, of course, is in the large quantity of magnesium present in the bones. It is assumed that the magnesium is deposited there as a result of growth processes taking place in the parenchyma of the skeletal tissue.

However, magnesium salts, introduced into the body, do have a marked influence on certain physiological processes. In the chapter on saline cathartics, magnesium action is discussed at length in relation to the function of the alimentary canal. More recently, through the work of Meltzer and Auer,¹ it has been pointed out that there is an antagonism between magnesium and calcium salts when these are introduced into the circulation. When, for example, magnesium chloride is injected into the circulation, animals so tested exhibit a rapid succession of pharmacological phenomena, quickly passing to a narcotic-like condition. Rabbits, for example, at first show accelerated respiration, then lose muscular control, fall over on the floor, and if left alone soon die. If, at the height of the narcotic stage, calcium chloride be injected into the circulation, the unfavorable condition is quickly removed and the animal will recover, gain its feet, and, in the case of the rabbit, begin eating almost immediately. This is an extremely striking phenomenon. The explanation offered by the authors is that magnesium has a narcotic effect, which is anesthetic in character.

Guthrie and Ryan² advocate a different explanation, namely, that magnesium has a curare-like effect on motor nerve endings. It is this action which destroys the motor control of the animal, and when not antagonized, of respiration itself. The introduction of calcium into the circulation antagonizes the curare-like action and the animal quickly regains control of its skeletal muscles.

Magnesium, instead of producing a primary anesthesia, in reality produces a primary stimulation. This is shown by accelerated respiratory movements and more sensitive reflexes. The stimulating effect passes over into a paralysis with the loss of nerve function.

¹ Meltzer, S. J., and Auer, John: *American Journal of Physiology*, Vol. XIV., p. 366.

² Guthrie, C. C., and Ryan, A. H.: *American Journal of Physiology*, Vol. XXVI., p. 329, 1910.

So far as the motor apparatus is concerned this undoubtedly, as Guthrie and Ryan have emphasized, depends upon the action of these salts at the motor nerve endings. They state that: "Results show that magnesium salts in common with numerous other crystalloids exert a very decided stimulating action when applied directly to the exposed trunk of a sciatic nerve of an otherwise intact frog. Indeed magnesium chloride stimulated more powerfully than certain other of the substances."

They are inclined to consider the action of these salts, magnesium included, from the standpoint of interference with the oxidations during nutritional changes, i.e., as asphyxial in character.

It is well known that certain toxins, particularly tetanus toxin, produce their poisonous effects by a hyperstimulation of the nervous motor mechanism. Since this is the point which is depressed by the magnesium salts, it is obvious that injections of magnesium chloride solutions, under this special toxic condition, would lead to a reduction in irritability of the motor end apparatus, i.e., would show antagonism against tetanus toxin. This particular fact has been made use of in clinical¹ practice in the saving of life after tetanus had developed. It apparently gives the body a respite in which the tissues may sometimes successfully continue the process of developing antitoxins.

III.

Barium and Strontium.

Barium and strontium salts, which belong to the calcium-magnesium group chemically, have proven quite interesting from a pharmacological point of view. Barium, in particular, introduces certain changes, comparable in character to the reactions of digitalis. Barium has already been treated, see page 174. Strontium, however, is of little significance pharmacologically.

¹ Kocher, T.: *Correspondenz-Blatt für Aerzte*, Basel; Vol. XLII., p. 969, 1912. Abstract in *Journal American Medical Ass'n*, Vol. LIX., p. 1496, 1912.

CHAPTER XLII.

THE SALINE CATHARTICS.

Under the heading of alkali metals and the alkaline earths we have discussed the physiological action of a number of salts. Some of these salts are characterized by their ready solubility and the facility with which they are absorbed, while others, sometimes less soluble, are characterized by the difficulty with which they are absorbed from the alimentary tract. Certain of the salts of this latter group produce, by virtue of their physical and chemical characters, special actions on the alimentary canal itself. This group is called the saline cathartics. The saline cathartics hasten evacuation of the bowels. This is accomplished in part by the action of physical characters of the salts, but also in part through their chemical properties.

Of the saline cathartics the most important and commonly recognized are sodium sulphate, known as Glauber's salt; magnesium sulphate, known as Epsom salt; and sodium potassium tartrate, known as Rochelle salt. Beside these specific salts any sulphate, citrate, tartrate, or phosphate of sodium, potassium, magnesium, or lithium will produce saline catharsis, though of course with greatly varying intensities of action.

I.

Nature of the Action of the Saline Cathartics.

An analysis of the nature of saline catharsis must rest upon an understanding of the physiology of the alimentary tract. Foods that are taken into the alimentary canal undergo a process of solution and absorption. The solution is accomplished largely by virtue of the action of enzymes introduced into the canal by the various alimentary secretions, saliva, gastric juice, pancreatic juice, bile, etc. Absorption takes place along the full length of the alimentary tract, occurring more rapidly through the wall of the small intestine and the upper part of the large intestine.

Food is moved along the alimentary tract as a result of the

muscular contractions of its walls, especially by the contractions which are peristaltic in character. Both secretion and the muscular movements of the alimentary tract are under complicated nervous regulation, a part of which at least is carried out through local reflex mechanisms. As the algebraic result of the four factors, i.e., quantity of food; rate and quantity of secretion; rate and time of absorption; and rapidity of the passage of the food along the alimentary tract, there will be a certain quantity of content of a certain consistency which will reach the lower portion of the large intestine, the descending colon. Under the control of the reflexes of defecation this residue will pass into the rectum and be evacuated from the canal. Anything either normal or pharmacological, which will vary one or more of the above four factors, will influence either the character or volume, and through these or by other action will stimulate the defecation reflex, hence determine the rate of discharge of the residue of feces.

The saline cathartics influence all these factors except the first, namely, the quantity of food. This we will undertake to explain. The typical saline cathartics, the sulphates, citrates, and tartrates, are characterized by non-diffusibility or at least retarded diffusibility. When these salts, therefore, are introduced into the alimentary tract the first and most striking influence noted is that upon the volume of the content of the bowel. Relatively little influence is exerted in this regard in the stomach, but a profound influence in the intestine, especially the small intestine. The presence of non-absorbable ions gives a permanent condition producing osmosis, which in this instance will tend to draw water from the mucosa into the tube of the intestine. Particularly is this true while the concentration of the salts is hypertonic to the body fluids and tissues. In fact, the rate of transfer of fluid is in fairly close proportion to the concentration of the non-absorbable ions. The sulphates, for example, are absorbed slowly and with marked difficulty. They produce, therefore, a withdrawal of water from the blood and tissues. This increases the volume of the alimentary content. If the volume becomes great enough to mechanically distend the intestine that will in itself stimulate the muscular mechanism and therefore cause an increase in the peristalses, thus hastening the driving of the content down the alimentary tube. The net result is that the volume of food, fluid, etc., is passed along the alimentary canal more rapidly than normally and reaches the rectum in a more fluid form.

The rate at which the above physical factor acts is largely de-

pendent, so far as the particular saline is concerned, upon the amount and concentration of the salt used. There is another factor, however, and that is the condition of the body as regards its normal content of water. Experimentally it is shown that if an animal be restricted in its allowance of water and fed a comparatively dry food for say 24 hours or more, its tissues become somewhat hypertonic. Under this condition of the body the non-diffusible saline cathartics act more slowly, or fail of purgation.

All substances which extract water from the mucous membrane of the alimentary tract have some degree of irritant influence on the mucosa. This irritant influence may vary greatly in intensity, depending not only upon the character of the salt itself, but also upon its concentration, and upon whether or not the stomach and intestine are relatively free of food at the time, i.e., intimacy of contact. A concentrated solution of a cathartic salt, or still better, an undissolved salt, will withdraw water from the mucosa of the stomach, where the salt first comes to rest for a time, so rapidly that the cells become quite hypertonic. This produces local irritation, and in many cases leads to marked reflex stimulation, accompanied by a burning sensation, sometimes nausea and vomiting. But this action of the saline cathartics is not vigorous enough to produce an inflammatory process. The action of this factor of irritation, especially in the duodenum and the upper lengths of the small intestine, may lead to quite profound reflex stimulation of the peristaltic mechanism of the canal. This increase in peristalsis may be great enough to lead to evacuation of the bowels within 15 or 20 minutes after the salt is taken, whereas an evacuation from the pure osmotic action would not ordinarily take place under 2 or 3, and usually more hours.

Any irritation of the gastric mucosa will inevitably reflexly accelerate the secretions not only of the salivary, but also of the gastric glands. Probably the pancreatic gland, too, is reflexly stimulated by irritation of the gastric and of the intestinal mucosa. It follows that there will be a great increase in the total volume of the gland secretions poured into the alimentary tract, and these will add to the quantity of the content. Ordinarily the sum total of the volume of the secretions of the alimentary tract will amount to some 3 or 4 liters per 24 hours, i.e., saliva 800 to 1000 cc., gastric juice 1000 to 2000 cc., bile 500 to 700 cc., pancreatic juice 600 to 800 cc. Under the stimulating effect of a concentrated cathartic these quantities are correspondingly increased.

We have, therefore, as a result of the general action of the saline cathartics the possibility:

1. of lowering the rate of absorption.
2. of extracting fluid from the mucous membrane.
3. of stimulation of the alimentary glands to increased secretion.
4. of stimulation of the peristaltic movements, thus hastening the content along the tube.
5. of stimulating the reflex mechanisms of defecation.

A salt that typically produces the first four of these processes will of course more quickly lead to purgation.

1. **Sodium sulphate.**—Glauber's salt or sodium sulphate dissociates into the readily diffusible sodium cation and the almost non-diffusible sulphate anion. If solutions of isotonic concentration are taken by way of the mouth they hinder the normal process of absorption. This factor alone would produce a seemingly more liquid content of the intestine, which is, of course, only a secondary result of the failure of normal absorption. But hypertonic sodium sulphate solutions cause some positive abstraction of fluid from the alimentary mucosa. The result is that there is an addition to the amount of fluid present in the alimentary content instead of a decrease as in normal absorption. The net results of the action of this positive factor is a mild catharsis, even were no other factor involved.

However, sodium sulphate stimulates the neuro-muscular mechanism involved in alimentary peristalsis. This can be shown if one performs the Moreau experiment by introducing sodium sulphate into the primary loop of the intestine. In this instance he will find that vigorous peristaltic contractions are set up almost immediately, in fact making it difficult to fill the loop with the fluid without external pressure. This is in contrast to the behavior of other cathartic salts in this regard. It is this vigorous intestinal contraction that produces the griping pain so often noted when Glauber's salts are used therapeutically. The effect is due to the direct stimulation of the mucosa, which leads to a reflex through the local nervous mechanism controlling the contractions of the intestinal wall.

Under the above discussion the action of sodium sulphate is explained as due to two processes: osmotic extraction of fluid from the mucosa and increase in physiological activity of the muscular walls. Hertz, however, has revived the theory of stimulation, which was advocated by MacCallum some years ago. Hertz's¹ studies indicated

¹ Hertz, A. F., Cook, F., and Schlesinger, E. G.: *Guy's Hospital Reports*, Vol. LXIII., 1901.

that watery stools from sodium sulphate did not contain an increase in the sulphate ions, in fact showed that the sulphates excreted by the feces were found only several hours after the first watery stool. On the other hand, there was a marked excretion of sulphate by the urine within eight hours after the taking of the salt. These

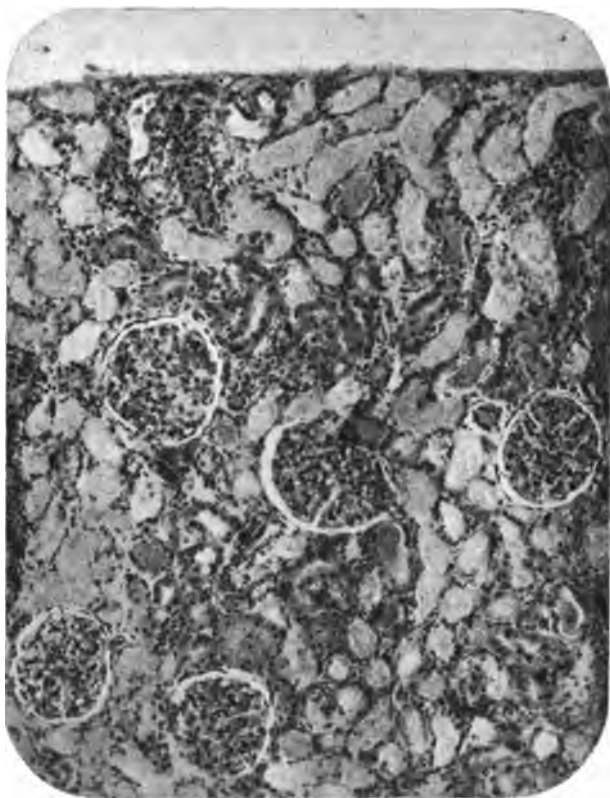


FIG. 69.—The effect of sodium tartrate upon the structures of the kidney. Necrosis involves every convoluted tubule. The glomeruli are normal. From Underhill, Wells, and Goldschmidt.

factors he says indicate that, “The semi-fluid character of the first stool was not a result of water being extracted into the intestine by the salt.” He emphasizes the point of view of Aubert, that after absorption the salt acts on the neuro-muscular mechanism of the colon rather than on the small intestine, producing an increase of motor and secretory activity. The sodium sulphate influence on intestinal movements is admitted and strongly emphasized, but that it is an

effect occurring only after absorption is at present a debatable question.

2. **Sodium potassium tartrate.**—The double salt of sodium and potassium tartrate owes its cathartic action to the low diffusibility of the tartrate anion. The cathartic action of this salt is milder than that of sodium sulphate. It does not produce such vigorous intestinal muscular contractions, hence is relatively bland in its effects. The anion in this case is slowly absorbed, but unlike most organic acid radicles, is not readily oxidized in the body. It is slowly excreted by the kidney unchanged. But while the tartrate is unchanged, one cannot say as much for the kidney after the tartrate has passed. Underhill, Wells, and Goldschmidt¹ have quite recently shown that tartaric acid is vigorously toxic for the renal tubules, producing marked nephritis with extensive necrosis. Curiously enough the glomerular capsules escape the injury, apparently due to the fact that they are not the main excretory organ for this injurious organic acid. The authors have given both morphological and physiological evidence for the contention offered. More recently Pearce and Ringer² have re-investigated the action of the tartrates in the production of experimental nephritis. Their conclusions from experiments on dogs are expressed in the following quotation:—

“The administration to the dog of tartrates, by mouth, intraperitoneally or subcutaneously, causes a severe renal disturbance, characterized by albumin and casts in the urine and diminished flow of urine or complete anuria. The urine passed before complete suppression is water clear of low specific gravity, and the solid constituents are greatly decreased. The most striking histological change in the kidney is necrosis of the convoluted tubules, with fatty changes in the loops of Henle and sometimes also in the collecting tubules. Exudative glomerular lesions occur in about half the animals with tubular lesions.

“The mode of administration does not influence the character of the renal lesion, except in as much as diarrhea, following administration by mouth, may cause rapid removal of the salt from the intestine, and thus by reducing the amount of absorption prevent the severer types of lesion.”

It has not yet been determined how toxic the tartrates are for

¹ Underhill, Wells, and Goldschmidt: *Journal of Exper. Medicine*, Vol. XVIII., p. 317, 1913.

² Pearce, R. M., and Ringer, A. I.: *Journ. Medical Research*, Vol. XXIX., p. 57, 1913.

the alimentary mucosa. The current view that they are mild and non-toxic should now be questioned on account of the action demonstrated on the renal parenchyma. It is probable that the mucosa does not escape an influence comparable to that observed in the kidney. If so its cathartic action of sodium and potassium tartrate more nearly approaches the character of that of the vegetable purgatives than other members of this group.

3. **Magnesium sulphate.**—Magnesium sulphate owes its saline purgative action to the slow diffusibility of both the positive magnesium and the negative sulphate ions. Magnesium is absorbed from the alimentary canal with difficulty, and we have already seen that the sulphate ion is greatly retarded in its passage through the intestinal wall. Therefore the presence of this salt produces a very effective condition of interference with the ordinary absorptive process. The content of the alimentary tube is kept relatively constant in fluid during its passage toward the colon. If the magnesium sulphate is comparatively concenetrated, then the hypertonic solution will draw fluids from the intestinal mucosa, as has already been described. The salt is not strongly irritant to this membrane and we may assume here a more vigorous physical action than with other members of the salts. The intestinal content reaches the colon in a more fluid form and in greater bulk and this leads to the cathartic action. The comparatively non-irritant qualities of magnesium sulphate make this salt a sufficient one for mild catharsis. If highly concentrated solutions in too great amount be used, then there is greater absorption of the salt itself, a process that may be sufficient to carry enough into the circulation to produce its specific depressant action. The systemic action has already been described, page 313. When such increased absorption occurs there is a tendency to suppression of intestinal peristalsis and to the appearance of a degree of the toxic action of the magnesium ion, as manifested on the respiratory mechanism and the skeletal muscular complex.

In the case of magnesium sulphate a process of precipitation and elimination of the magnesium cation goes on in two ways; first, through the formation of carbonates from the carbon dioxide content of the blood, and second, by the formation of magnesium soaps from the fatty acid liberated during fat digestion. Each of these compounds reduces the magnesium to a molecular basis. The sulphate ion, under these conditions, is slowly absorbed and combines with hydrogen ions derived from the blood and tissues to form acids, or with the alkaline bases to form soluble sulphates, which are ex-

creted through the kidney. Either process tends to work against the alkalinity of the blood and toward relative acidosis.

MacCallum¹ has studied the cathartic action of the magnesium salts by the method of hypodermic injections. He came to the conclusion that the magnesium sulphate produced its cathartic effects through the direct stimulation of the secretory nerve mechanism, controlling the flow of fluids into the colon and the mechanism of defecation. He describes the appearance of catharsis as occurring after a constant and rather short time interval, thus throwing doubt on the osmotic properties and relations described above. Hertz has to some degree supported this view of saline catharsis in general as previously mentioned. However, this work of MacCallum's has been questioned more recently, and it has been suggested that his position is erroneous, largely through the unfortunate choice of rabbits as investigation animals. Rabbits are ill adapted to this type of experiment. One may, in the circumstances, take a conservative position.

The introduction of magnesium sulphate by way of the mouth is said to be favorable in certain types of edema. In fact, magnesium sulphate may, through its vigorous extraction of fluid from the mucosa, quite strongly reduce the water content of the tissues. Even the normal tissues may be rendered hypertonic. If the tissues are already hypotonic from edematous processes, then saline catharsis favors the elimination from the body of such injurious materials as toxins, poisons, etc. The carrying out of the body of a large amount of fluid by either the alimentary canal or the kidney will of necessity wash out large quantities of such special materials. If the toxins are derived from the putrefying masses in the alimentary canal, then, of course, the beneficial influence consists largely in removing the source of the injurious agency. It is this latter factor which is utilized by the clinician in the course of many infectious conditions of the alimentary tract. It would seem, at first sight, that if the tract were already inflamed and in the over-active condition expressed by diarrhea, the giving of a purgative of any kind would be contraindicated. But the mild saline purgatives do not add much to the pathological inflammatory process and they have the further advantage that their action begins at the upper or duodenal lengths of the alimentary tract, hence they tend to dislodge and remove the putrefying or infecting agency wherever it may be located. The specific poisonous action of the magnesium ion of magnesium sulphate and the tartrate ion from the tartrates justified the caution against the use of these

¹ MacCallum: *American Jour. Physiol.*, Vol. X., 1903.

drugs in conditions of marked inflammation or possible necrosis of the alimentary canal. Where the protective mucous membrane of any surface has for any reason been injured there is always the danger of the absorption of such toxic ions, an absorption that may produce very unfavorable, even dangerous, results.

4. **The saline cathartics as enemas.**—The discussion of the action of the saline cathartics presented above is based on the changes which follow their introduction into the alimentary tract by way of the mouth. Clinically speaking, there are many conditions in which evacuation of the bowel is desired, yet in which this route is unfavorable or prohibited. Rectal injections or enemas are utilized under these conditions. Pure cold water is one of the most active agencies for this purpose. It stimulates mildly and therefore sets up rectal peristalsis, thus producing evacuation. On the other hand, if the content of the rectum is relatively dry and firm, a slow absorption of water by the fecal matter may be desired in order to soften and facilitate the evacuation. In this case enemas of any of the above saline cathartics, or, in fact, of the more mildly acting saline soaps, may be used. Sodium sulphate favors the development of peristalsis, which may in some cases amount to rather violent tenesmus. Magnesium sulphate facilitates a relatively slow secretion of considerable fluid into the bowel, the consequent softening of the content, and the development of mild defecatory impulses. The use of salines as enemas rests chiefly on the factor number five, previously mentioned, i.e., the stimulation of some portion of the reflex mechanism controlling the act of defecation.

For agencies which act particularly on the large intestine, the reader is referred to the discussion of the vegetable purgatives.

CHAPTER XLIII.

ALKALIS AND ACIDS.

The displacement of the usual salt anions, i.e., chloride, bromide, sulphate, etc., by hydroxyl, OH, and the substitution of the usual salt cations, i.e., sodium, potassium, magnesium, etc., with hydrogen, H, gives to these substances properties whereby they are peculiarly toxic. The alkalis, especially in the stronger solutions, are particularly caustic. The acids, on the other hand, are many of them precipitants to proteins, and in more concentrated solutions also caustic, therefore toxic.

I.

Alkalis.

The alkalis of most general interest are the hydrates of sodium, potassium, ammonium, calcium, etc. The carbonates of these bases are alkaline in reaction, but this is due to the fact that the dissociated carbonate anion tends to combine with one hydrogen of water, setting free hydroxyl ions. Hence in both cases the alkalinity and, therefore, the caustic action is due to the hydroxyl ion. The action of the cation of the alkalis is the same as in the corresponding salts which have already been discussed.

A mild degree of alkalinity is normal to living protoplasm. The physiological fluids are slightly alkaline in reaction and blood plasma from the presence of sodium carbonate and disodium phosphate normally has the percentage of alkalinity 182 to 218 mgr. NaOH per 100 cc. of blood, Simon. The blood plasma holds tenaciously to the alkaline reaction. The chemical reactions of protoplasm take place best under this condition of mild alkalinity. If the alkalinity is overcome and the reaction reduced to acid, then the physiological processes of protoplasm are hindered or cease altogether. A slight increase in alkalinity above the normal limit hastens physiological activity. Hydroxyl ions promote hydration processes in the tissues, hence the favorable action just mentioned is in all probability due to a corresponding increase in the fluidity and permeability of the tissues.

The favorable limits or range of increase in alkalinity are re-

stricted. The higher concentrations tend to produce injurious hydrolysis of the tissues. The alkalis are therefore peculiarly caustic.

1. **The cauterizing action of the alkalis.**—Sodium hydrate in 5 per cent. solution applied to the skin quickly leads to hydrolysis of the corneous layers. The solution readily penetrates to the deeper layers of the corium, producing dissolution and corrosion. The concentrated solutions of the hydroxides kill, but do not dissolve the tissues until the alkali is diluted, at which time solution quickly takes place. Many violent accidents constantly occur from this action of the alkalis. If the corrosive agent is not removed or neutralized, then it continues to penetrate deeply into the tissues and may lead to the death and dissolution of extensive areas.

2. **The physiological action of the alkalis.**—Alkaline salts of the hydrates produce changes in physiological responses of the body in two ways. One is through the mild stimulation of reflex nervous mechanisms, especially in the mouth and gastric region. The second is through the change in the degree of alkalinity of the body protoplasm. When alkalis, carbonates or hydrates, are taken by way of the mouth, the first effect is a neutralization of the acid gastric juice, accompanied by a mild reflex stimulation of the gastric mucosa. When these solutions pass into the intestine they favor the normal alkalinity that already exists in this region. Alkalis are readily absorbed. When they pass into the blood stream and are distributed throughout the body they favor protoplasmic processes chiefly through their favorable influence on oxidations. Muscles contract more vigorously, glands secrete more efficiently, as for example the increased quantity of the bile.

However, once in the circulation, the added alkalinity is quickly adjusted by virtue of the ability of the tissues to neutralize any marked variation from the normal per cent. of alkali or acid. As an example, one needs only to note the excess of carbon dioxide constantly being formed, which can take up and balance any increase in the alkalis. The alkalis are readily excreted through the kidney, and it is said that uric acid excretion is increased by the alkalis. The body can handle considerable amounts of alkali, enough to reduce the normal acidity of the urine or even produce a slight alkalinity. Clinicians utilize this factor in combating those conditions of hyperacidity present in certain types of acidosis.

II.

Acids.

The mineral and the organic acids may be considered together, though they vary strikingly in certain properties. On the whole, the acids are generally toxic to protoplasm. The mineral acids are peculiarly so. Although hydrochloric acid is a normal constituent of at least one body fluid, i.e., gastric juice, yet it is one of the most toxic of the group. However, in the percentage represented in the gastric juice the hydrochloric acid is mildly antiseptic. In fact, this antiseptic action is normally great enough to destroy large numbers of bacteria, which would otherwise enter the lower part of the alimentary tract, and become positive sources of disease in the body. Nitric acid is strongly oxidative and precipitative, as is also sulphuric. Both are corrosive in concentrated form.

If the stronger mineral acids are applied to the skin they produce at once precipitation of the protein constituent and death of the epidermis. The precipitation of the tissues tends to hinder the further diffusion of the acid, yet when not neutralized there is slow diffusion and destruction of the deeper tissues. The process is violently irritant, hence there is great pain from the continued hyperstimulation, often leading to nervous shock and collapse. The mineral acids exert the same type of cauterizing action on the mucous membranes as on the skin, that is, there is a tendency to precipitate proteins, resulting in the forming of layers or coats, which delay the diffusion of the acid into the deeper parts. The reflex effects of this type of corrosion on the mouth and alimentary tract are tremendous. There occurs an over-stimulation of the great medullary centers leading ultimately to vascular dilation, cardiac irregularity, and in some cases collapse with the accompanying shock.

The organic acids are also strongly irritative, but not so corrosive. In the body they more quickly become diluted and certain of the acids are oxidized; for example, acetic, citric, etc. Among this group tartaric acid is not readily oxidized, therefore its irritative properties continue up until the time of complete elimination.

1. **The action of dilute acids.**—The normal 0.2 per cent. hydrochloric acid present in the gastric juice performs several interesting functions. These have been described by Cannon in his discussion and demonstration of the acid closure of the pylorus and of the cardia. The presence of 50 cc. or so of 0.2 per cent. hydrochloric

acid suddenly introduced in the upper end of the duodenum leads to local reflex contraction of the pyloric sphincter, and, therefore, closure of the pylorus. The cardiac sphincter reacts in much the same way. Both instances are examples of reflex stimulation of sensory structures in the mucosa by the dilute acid. Dilute acids act in like manner in other parts of the alimentary tract, as for example the stimulating effect of acetic or citric acid in the mouth. A taste of lemon juice is sufficient to set up a quite vigorous secretion of saliva. The same reflex mechanism can be set into action by dilute inorganic acids, hydrochloric acid, sulphuric, etc. The fruit acids play an important physiological and pharmacological rôle in the body by virtue of this property.

Dilute acids, both organic and inorganic, are readily absorbed, possibly in part by virtue of the formation of acid proteins. When introduced into the circulation the acids meet the alkalis resulting from tissue metabolism and are either oxidized or neutralized. Fortunately the body possesses a complex and adequate mechanism for doing this very thing. A quantitative excess of acid becomes injurious since it leads to the precipitation and destruction of proteins and a corresponding freeing of basic nitrogen for the elimination of the acid. However, before this takes place a considerable excess of acids may be taken care of by the body by virtue of the conversion of neutral salts into acid salts, such as the conversion of sodium carbonate into bicarbonate, monohydrogen phosphate into dihydrogen phosphate, etc.

Any free ammonia in the body fluids or tissues fixes acid ions, forming the corresponding salts. Ammonia nitrogen is always an available base for neutralizing excess of acid ions. Acids, therefore, tend to increase the ammonia output in the urine, and in direct ratio to reduce the urea output by the equivalent interference with the usual formation of urea of ammonia wastes.

The kidney excretes acids largely as acid salts. If the quantity is great enough to lead to an excess of acid there will be a positive irritation and necrosis of the renal epithelium, which, of course, is unfavorable.

The organic acids, like acetic, citric, etc., are oxidized by the body. Under normal conditions, therefore, these acids are eliminated without injury to the organism. Tartaric acid is an exception in the group. If for any reason the oxidative power of the body is reduced, then a portion of the organic acids may pass through the body insufficiently oxidized and prove injurious. The therapeutic condi-

tion of acidosis is a condition in which, for reasons of incomplete oxidations an excess of acids occurs. These acids may be derived from the incomplete oxidation of fats on the one hand, or of carbon-hydrates on the other, as well as from acids taken into the body from without.

CHAPTER XLIV.

OXIDIZING AGENTS, OXYGEN, PEROXIDE, ETC.

I.

Oxygen.

That oxygen is necessary to the life of animal tissues was long ago established. The part played by oxygen in respiration in general was made known by the ancient experiments of Lavoisier and of Priestly. In the mammalian body the amount of oxygen is kept relatively near the saturation point in the animal fluids. That is, considering the partial pressure of oxygen in the air it is found that the amount of oxygen in the blood plasma and in the body lymph is high and comparatively constant. It is assumed in physiology that the interstitial oxygen is held in some form of fixed compound with the living protoplasm. Such a favorable condition is made possible only by the development of respiratory pigments, in the case of man and mammals the hemoglobin.

Experiments on isolated tissues readily demonstrate the necessity for oxygen. Loeb has given special emphasis to this point, calling attention to the fact that if free oxygen is removed from about developing eggs of marine invertebrates the developmental process slows or ceases. It is immaterial whether the oxygen is removed directly or its utilization prevented by the presence of some salt, as for example sodium or potassium cyanide. The various methods for studying the isolated organs, such as portions of the intestine, uterus, etc., all provide for an adequate supply of free oxygen in contact with the tissue. When this free oxygen is withheld, then the normal physiological processes are reduced or tend to disappear. Under ordinary physiological conditions an oxygen environment, represented by the atmospheric pressure at ordinary levels, is sufficient. When this percentage is reduced by extreme heights, as in aërial navigation, it may happen that the percentage of free oxygen is below the necessities of the body and unconsciousness and death may result.

A diminished percentage of oxygen acts as a stimulus to the nervous tissue, particularly the respiratory center, though one must remember that the condition is usually associated with an increase of

carbon dioxide, which stimulates the respiratory center even more strongly. This particular center is, in a way, a special case. The accelerating influence of oxygen-lack occurs only within restricted limits. If the deficiency of oxygen is too great, then even the respiratory center loses its irritability and becomes paralyzed. The recent work of the Pike's Peak Expedition¹ served to show that there is a certain amount of adaptation which the body can make to rarefied atmospheres. If, under such an environment, physical exertion is reduced to a minimum life is maintained with a much lower percentage of oxygen in the air than would otherwise be required.

1. **Effects of increase of oxygen.**—The respiration of pure oxygen does not increase the amount of available oxygen in the body to the extent that one would suppose. Normal respiration of ordinary air is adequate to saturate about 0.9 the hemoglobin, hence we have only the remaining 0.1 as a variant for increasing the amount of oxygen carried into the tissues. Of course in certain diseases or in certain environmental conditions of a physiological nature there is great reduction in the total amount of oxygen secured by absorption. Under these circumstances the substitution of oxygen for ordinary air will prove favorable. The higher percentage of oxygen respired will facilitate the amount absorbed by increasing the difference in the absorption level. Thus, in cases where the active portion of the lung is reduced to a fraction of its normal, there might possibly be enough oxygen absorbed from the pure gas to supply the physiological needs of the body, where such would fail if ordinary air were breathed.

In the mammalian body the percentage of oxygen in the blood plasma and in the lymph of the capillary bed is below the saturation point. In the tissue itself it is generally assumed that the free oxygen is fixed as soon as it enters the protoplasm. It has been stated above that the cutting off of the supply of free oxygen quickly stops protoplasmic activity. Its readmission leads to a re-establishment of metabolism, a point proven in the development of fertilized egg cells, and more fully elucidated by Loeb. If pure oxygen is made to saturate the lymph bathing a tissue, that will facilitate or stimulate the intensity of physiological processes. Though the excess of oxygen in contact with protoplasm increases oxidative

¹ C. G. Douglas, J. S. Haldane, Y. Henderson, and E. C. Schneider: *Philosophical Transactions of the Royal Society, Series B*, Vol. CCIII., pp. 185-318, 1912.

processes it must not be forgotten that excess of oxygen in the respiratory gases does not necessarily provide this excess around the tissue itself. It seems that this point may be over-emphasized because of the general assumption of the contrary proposition.

II.

The Peroxides.

Of all the oxidizing agencies the peroxides are probably the simplest and most active. Hydrogen peroxide, H_2O_2 , serves as an ideal representative of the class. The oxidizing power of hydrogen peroxide on living tissues is recognized in the therapeutic use of the chemical for sterilizing and disinfecting purposes. A solution of 1 to 10,000 in water is sufficient to kill ciliate infusoria in from 15 to 30 minutes (Paul Bert). Hydrogen peroxide in the stronger solutions prevents development and leads to the destruction of many forms of bacteria, in particular the anaerobes.

Hydrogen peroxide brings about oxidation in certain types of chemical reaction where the presence of ordinary atmospheric oxygen fails of reaction. In the human body there are reductions which occur in the presence of normal protoplasm in particular groups of chemicals the oxidations of which cannot be produced outside of the body except in the presence of hydrogen peroxide. This has led physiological chemists to certain theories of auto-oxidation. These views, together with an illustration, are presented distinctly in the following quotation from Dakin¹:

"It is generally believed that living cells contain labile substances capable of taking up molecular oxygen from the oxyhemoglobin of the blood with the formation of unstable peroxides possessing marked oxidizing properties. Schönbein, and later Bach, have shown that a large number of substances of the most diverse kinds when undergoing slow oxidation yield substances giving the reactions of hydrogen peroxide.

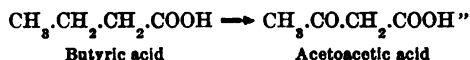
"In addition, Baeyer and others have actually isolated a number of superoxides and substituted hydrogen peroxides derived from many different types of aldehydes and ketones. It certainly appears likely that substances of this type are concerned with the oxidations of substances in living tissues, and indeed such knowledge as has been

¹ Dakin, H. D.: *Oxidations and Reductions in the Animal Body*. New York, p. 7, 1912.

derived from a study of the various oxidations effected by enzymes found in the living cells strongly supports such a supposition. The occurrence of certain metallic salts, especially those of iron and manganese, in conjunction with certain vegetable oxidases, and the extraordinary influence they have upon the ferment activity, is paralleled by the catalytic action of these same salts in accelerating oxidations *in vitro* by means of hydrogen peroxide.

“ Within the last few years other evidence has been secured in favor of the belief of the formation of unstable superoxides as the active oxidizing reagents of the body. If the hypothesis of superoxide formation is correct, one would expect a certain similarity between the oxidations effected in the body and those brought about by the simplest superoxide, namely hydrogen peroxide. As a matter of fact, an extraordinarily close similarity as regards the types of reaction exists between the two sets of phenomena. Thus the normal saturated fatty acids in the body undergo oxidation in the β -position, butyric acid yielding acetoacetic acid—a truly remarkable change.

“ Hydrogen peroxide alone of all the various chemical oxidizing agents brings about precisely the same reaction:—



A number of vigorously acting chemical oxidizing agents are very toxic to living protoplasm. Of these may be mentioned chromic acid, permanganic acid, chlorine, bromine, arsenic acid, phosphorus, all of which owe their extreme toxicity to the formation of fast oxygen compounds. These are outside the field of oxidizing agents in the physiological sense, and are discussed under the head of Toxic Action in the appropriate place.

M. The Salts of the Heavy Metals.

CHAPTER XLV.

THE GENERAL REACTIONS OF SALTS OF THE HEAVY METALS.

Salts of metals, roughly classified pharmacologically as the heavy metals, have certain general reactions which influence the functions of the mammalian body. There is no strict line to be drawn from the pharmacological point of view as regards the salts included in this group. But the more important metals included in the discussion are: Copper, lead, zinc, sulphur, phosphorus, iron, mercury, silver, and bismuth. Beside these, a number of other members of the chemical group are pharmacologically active but in no way peculiarly distinct from the action of the members of the group chosen, and of no special practical significance. Chiefly for these reasons they are not included in this discussion.

1. **The formation of metal albuminates.**—What changes the different salts of a given metal will induce and the comparisons of the reactions of salts of the different metals depend upon several chemical and pharmacological factors which will be briefly discussed.

The most typical reaction of the salts of this group consists in the formation of albumin compounds. Most of the heavy metals react with different proteins and protein-like substances to form the corresponding albuminates. In this regard the organic substances act like acids, displacing the acid in combination with the metal. For example, lead acetate in contact with protoplasm forms a soluble lead albuminate of the protein moiety of the protoplasm, at the same time setting free acetate with the coincident formation of acetic acid. The same may be illustrated by silver nitrate, mercuric chloride, etc.

The intensity and rapidity of this reaction depend upon the solubility and the ionizing properties of the particular salt. If the salt is very soluble and ionizes freely, it will produce a more vigorous and rapid precipitation of protein and a corresponding greater pharmacological reaction if that protein is a constituent part of living protoplasm. Organic compounds of the metals are for this

very reason less intense in their actions than inorganic compounds.

In general the reactions of the salts of the heavy metals are astringent, stimulative, irritant, or corrosive. The action is not entirely due to the metal factor, but in some forms it is partly due to the action of the acid ion liberated.

The metal albuminate is in many instances soluble in excess of the albumin. Some organic compounds, as metal vitellinate, are generally soluble. Most metal albuminates when in small quantity are soluble in excess of the albumin. The different metals vary greatly in this regard. Albuminates of mercury are rather more readily soluble in excess of the albumin than are, for example, silver albuminates. Another factor in the human body that greatly influences the solubility of the metal albuminates is the presence of the salts of the alkaline earths. An insoluble excess of albuminate of mercury in neutral watery solution is readily soluble in a physiological saline solution. In the body this factor undoubtedly increases the solubility of not only albuminate of mercury, but of other organic compounds of the heavy metals. Sodium chloride is a constituent of every normal body fluid.

When a metal salt is brought into contact with an animal membrane, as an example the mucous membrane, the characteristic reaction with the formation of albuminate occurs. The reaction is more intensive at the surface of contact, and a layer of albuminate over the mucous membrane is the result. If this albuminate is not very soluble it forms a protective coating to the deeper structures. The film of albuminate forms a resisting membrane to the further penetration and absorption of substances in solution in contact with it. By far the most important constituent of this solution is the hydrogen salt of the acid ion set free when the albuminate formation occurs. If this acid be in itself a toxic and corrosive one, as in the case of mercuric chloride, then it will have its usual effect on the protoplasm. The film of protecting albuminate delays the diffusion of the hydrochloric acid, hence modifies its corrosive action. If the acid ion of the metal salt be comparatively non-irritant or oxidizable, as in the case of lead acetate, then the influence of the salt as a whole will be astringent.

In salts of this nature the concentration and solubility factors are of very great importance in the modification of the form of reaction of the tissues. Take, for example, mercuric chloride; if the solution is present in concentrated form, then the albuminate formed will be deeper, but the more concentrated acid ions liberated will penetrate

deeper and quickly, notwithstanding the presence of the albuminate. Inflammation will, of course, be induced. The more dilute solutions, for example the 1 to 1000, do not ordinarily induce inflammation unless held in contact with the tissue for a long time, notwithstanding the formation of a surface layer of albuminate. It is obvious that the difference between a stimulative irritant and a corrosive action with such a salt as this is bounded almost wholly by the concentration factor. The purgative salt, calomel or mercurous chloride, is a splendid example in this connection. Mercurous chloride is so slightly soluble in the alimentary canal that there are never at any one time sufficient ions present to produce more than a mild stimulative effect on the mucous membrane. Lead acetate is somewhat illustrative of this variation in the action of metal salts, since the acetate is comparatively less irritant than the chloride of the mercuric salts. Although lead acetate is readily soluble, the acetic acid formed during its dissociation and reaction in the tissue is not so strong in its toxic effects on the protoplasm. Hence the albuminate coat modifies the action of the acetate down to the point where the total effect is only that of a pure astringent. But in this case a larger quantity of highly concentrated solution of lead acetate may become irritant or even corrosive in its action. Instances of acute gastritis are on record, illustrating this point.

The salts of the organic compounds of the heavy metals, such as metal caseinate or soluble albuminate, are comparatively non-toxic. Although these salts are soluble, they ionize very slowly, if at all, and are, therefore, non-irritant. It is for this reason that the newer organic compounds of the heavy metals have been strongly recommended in order to displace the irritant and acute toxic action of the inorganic compounds.

Speaking generally, the pure metals, as such, are inert. This, however, is only a comparative truth. One may take a piece of iron, a copper coin, or a drop of mercury into the mouth, or it may be swallowed and pass through the alimentary canal with comparatively no injury. However, the alimentary tissues and fluids do dissolve traces of metal, apparently with the direct formation of albuminates. This is held to be the case with metal mercury. If the mercury be in fine division, as, for example, in blue mass, enough of the metal may be taken up to produce a typical mercurial reaction. The presence of hydrochloric acid in the gastric juices may, and probably does, induce this reaction with certain metals. A state of fine division of the metal would favor this solution in hydrochloric acid.

However, this point is based more on theoretical grounds than on the results of wide investigations.

In recent years the metals have been recommended and used in practical therapeutics, as in the colloidal solutions. Colloidal metals are in a state of fine division, and in this form become available for the formation of albuminates and may, in fact in some instances do, enter the body quite rapidly, and produce the usual and typical reactions.

2. The absorption of salts of the heavy metals.—Under the general heading of this division we may introduce the general underlying principles which, with minor variations only, hold for practically all of the heavy metals. The basis for these observations has already been laid in the discussion of the general action of the heavy metals.

Salts of the heavy metals are absorbed by the human body only through mucous membranes or from abraded surfaces, as, for example, wounds, ulcers, sores, etc. Absorption in any case is slow and occurs with difficulty. The very process of the formation of metal albuminates, as discussed above, for the time being delays or even stops the passage of those metals through any layer of living cells. In comparing different metals one can see at once that the rapidity of absorption in each instance will certainly depend upon the relative solubility of the albuminate formed. Since the albuminates are soluble in excess of protein, and that solubility is increased by the presence of salines, it is obvious that in the human body there are factors acting which are quite adequate to ultimately carry the metal into the circulation and thus distribute it throughout the body. The slowness of absorption is adequate to account for the fact that the heavy metals rarely produce acute general toxic symptoms. Not enough of the metal enters the system at one time to lead to the general reaction. Where apparent acute general toxicity occurs it is very apt to be complicated by the local reaction from the acute corrosion of a particular area, as, for example, in acute gastritis from the action of silver nitrate.

Absorption takes place with fair rapidity from extensive abrasions or ulcers. The slow and long continued absorption will ultimately introduce enough metal of most heavy metals to lead to chronic toxic action. Perhaps the most typical example of this kind of metal poisoning is that of chronic lead poisoning.

3. The distribution and excretion of the heavy metals in the body.—Under the action of the principles outlined in the preceding paragraphs, the salts of the heavy metals are introduced with more or

less delay into the general circulation. In the majority of cases this absorption is extremely slow, and scarcely detectable traces are thrown in the circulation in any short period of time. Once in the blood, the metals are distributed throughout the body. They do not remain long in the blood; in fact, they are rapidly removed. Apparently they are taken up by the epithelial tissue of the vascular bed and passed over to the adjacent parenchyma of whatever organ they come in contact with. The liver is no doubt an important depository for heavy metals. Higher percentages of the metals are extracted from the liver than from any other organ of the body, but the metals are deposited in practically all organs, especially glandular organs and organs rich in connective tissue.

The excretion of the metals takes place through all glandular structures. This includes not only the kidney, but the glands of the alimentary canal, and especially the alimentary mucosa. The mucosa of the large intestine has been proven to be a channel for the excretion of a number of heavy metals, possibly because the important metal precipitant, hydrogen sulphide, is present in this tissue in greater quantity than in other portions of the digestive tract. The slow excretion of the metals into the upper reaches of the alimentary tract brings about a condition favorable to their reabsorption. In fact, reabsorption occurs in greater or less degree with most all of the heavy metals. The net result is a cycle of reabsorption and reexcretion, oft repeated through a vicious circle which prolongs the general toxic action on the body tissues. It is this factor which so strikingly delays the final excretion of metals after their introduction into the body, a delay that is known to extend over several months. In the case of silver, the deposits in certain tissues, especially the subdermal connective tissues, become permanent, i.e., never dissolve.¹

With these general factors in mind, we may take up the more important individual metals of this series. The elements, iron, sulphur, and phosphorus, differ from the other heavy metals owing to the fact that these metals are present in normal protoplasm. They are, therefore, singled out and treated first in the series.

¹ Dr. Crispin has just reported an interesting case of argyria from the use of collargol, *Jour. Am. Med. Ass'n*, Vol. LXII., p. 1394, 1914. A laparotomy on this case revealed the interesting fact that the "tissues, muscles, and intestines had a bluish tinge." It is of further interest that the treatment of the case for another affection by 10-grain doses of hexamethylamine led to a clearing of the skin and to partial disappearance of the argyria.

CHAPTER XLVI.

IRON.

The numerous iron salts known to chemists are not of pharmacological interest as such. They for the most part ionize, in which process iron is set free as active cations. The physiological action of iron may be illustrated by consideration of ferric chloride.

1. *The normal relations of iron in the body.*—The most typical iron-containing substance in the mammalian body is hemoglobin, present primarily in the red blood corpuscles, but also in smaller quantity in the muscles, certain glands, etc. Hemoglobin has the distinction also of being the most complex organic molecule of the mammalian body. It has the enormous atomic weight of 16,660. Iron is also yielded, though only in smaller quantities, by the muscles, liver, skeleton, in fact by most of the tissues of the body. It is present only in traces and possibly some portion of the iron attributed to certain tissues may have been derived from corpuscles of the blood still in the vessels of the organ, especially the iron of analytical chemical determination. The iron of skeletal muscle is attributed to a definite pigment muscle hemoglobin. Whether this will hold for the iron of the liver is not so clear.

Many conditions arise in the body in which there is great destruction of the red blood cells with a corresponding loss of hemoglobin. This loss must be compensated for. In human diet the compensation is generally adequate through the iron content of the various materials of the food. In disease, for example in malaria, the iron may be so completely removed as to greatly weaken the individual concerned. In malaria the destruction of red blood corpuscles and the accompanying loss of hemoglobin may be so great as to lower the oxygen absorbing capacity of the blood for 50 to 70 per cent.

Iron seems to be intimately bound up with general metabolism. If iron chloride is administered in small doses, a total of 10 to 30 minims of the tincture of iron per day, it accelerates metabolism, acting very much as a mild tonic. However, the inorganic ferric chloride is metabolized with difficulty. In fact, it has been questioned as to whether or not this compound can be utilized by the

body. It is certain, however, that the administration of the inorganic iron is favorable and one is compelled to assume that it is either directly utilized or that it acts as an iron sparer. By this latter view the ferric chloride would serve the purposes of iron excretion, thus conserving to the tissues for further metabolism such iron as would otherwise be excreted.

2. Evidence of the absorption of iron.—A number of valuable experiments have been performed on mammals with the attempt to demonstrate the absorption of inorganic iron. If an animal be fed with an iron salt and after a sufficient time for absorption be killed and the alimentary canal be opened for its full length, and the mucous membrane painted with ammonium sulphide, it is found that two areas of the mucosa are blackened. The first one is in the upper portion of the small intestine, the duodenum; the second is in the lower portion of the colon and rectum. The experiments of Hall and others have given indication of the direct absorption of iron by the duodenum. It is not so clear whether the rectal iron is that being absorbed or iron on the way to excretion. Fistulas of the intestine have been established, and then iron fed on the assumption that any unabsorbed iron passing through the small intestine would be removed through the fistula without reaching the colon. Under these conditions iron is found in the content of the rectum, and it is assumed it reaches this point by excretion through the rectal mucosa.

3. Iron-protein compounds.—Iron, especially in the form of chloride, acts as a precipitant of proteins. In the normal relations in the body the iron is present undoubtedly as an iron-protein, of which hemoglobin is the typical example. This has raised the question as to the form in which the iron is absorbed. It seems probable that it enters into a protein compound with substances of the food or of the mucosa and is absorbed into the body as such.

Hall, by micro-chemical methods, has been able to demonstrate the presence of iron as such in the epithelium of the intestinal villi which he considers to be iron in process of absorption.

Basing the procedure on the tendency of iron to form organic compounds, numerous organic iron compounds have been introduced into therapeutics in the hope that in this form the chemical will be more available to the body. Some of these preparations are less objectionable to the taste and less astringent in their influence on the mucous membrane, but on the whole they do not seem to favorably improve the protoplasmic reactions of the body more than do the inorganic compounds.

4. **Astringent action.**—Iron chlorides have for a long time been known to be markedly astringent to the mucous membranes of the body. When taken by the mouth they have an acrid, “astringent” taste, and when swallowed in too large quantity lead to some reflex nausea and possibly vomiting. Owing to this local action there is a tendency to gastric inflammation.

The local astringent action of iron has given the perchloride a reputation as a styptic in cases of local bleeding. The iron in this case has its usual chemical action of precipitating proteins, and thereby tends to hasten blood-clotting and the formation of a mechanical coat that obstructs the bleeding. It is effective in this regard both for external wounds and in bleeding from the nasal or buccal cavities, or in some deeper portion of the alimentary tract. However, the practical use of iron as a styptic is now more or less superseded by other agencies, for example preparations of epinephrine.

CHAPTER XLVII.

SULPHUR AND THE SULPHUR COMPOUNDS.

In physiological chemistry we have already learned to know the importance of sulphur in the composition of protoplasm. All protein bodies contain sulphur, along with nitrogen, oxygen, hydrogen, and carbon. Sulphur is present in various proteins in from 0.3 to 2.2 per cent. Sulphur, therefore, is of an importance comparable to nitrogen in the reactions of protoplasm. The primary interest in the sulphur compounds is, therefore, physiological chemical. Among the questions of importance are the sources of sulphur and the forms in which it leaves the body through the excretions. The determination of the excretion of sulphur has come to be almost as important as the determination of nitrogen, in the light which it throws upon metabolic processes.

The consideration of the detailed reactions of a normal nature will have to be left for discussion in connection with physiological chemical questions. We give here only a brief discussion of the behavior of sulphur and sulphur compounds as such.

1. **Sulphur.**—Sulphur in its pure form is a very inactive drug. If applied to the skin or when taken into the alimentary tract by way of the mouth it undergoes comparatively little change, and is thrown out of the body as sulphur in the stools. A certain amount is transformed into hydrogen sulphide in the intestinal tract. As sulphides this sulphur is absorbed and makes its appearance in the circulation to be excreted as sulphates in the urine, or to some extent as sulphides through respiration, where it gives a characteristic disagreeable odor to the breath.

It is still an open question whether the display of neutral sulphur exerts any favorable action upon metabolism as such. Its presence in the alimentary tract acts as a mild cathartic, possibly contributing to the normal reactions of the bowel when this organ is relatively sluggish.

2. **Sulphides.**—The sulphides are somewhat irritant and toxic. If introduced into the circulation they lead to depression of function of both the nerves and the muscular tissue; from the latter action

they weaken the circulation, and from the former produce some slight degree of narcosis. Harnack¹ has described a type of convulsion in the frog following a toxic injection of hydrogen sulphide.

It is probable that the small proportion of sulphides formed from neutral sulphur in the alimentary tract tends to produce this characteristic change in the important nervous and muscular mechanisms of the body. Traces of sulphide formed during intestinal digestion would be toxic to the extent of their concentration.

3. **Sulphates.**—The oxidation of sulphur and sulphur compounds in the body is largely to the form of acid sulphur, the sulphates; and to neutral sulphur, the various organic compounds. The sulphates are eliminated from the kidney as such. Their excretion is in acid form, hence any great increase in the quantity of sulphur excreted in this form tends to produce a degree of mild irritation of the renal tissue. This condition has been mentioned under the chapter on Saline Cathartics.

4. **The organic sulphur compounds.**—A number of organic sulphurs are of some pharmacological interest. Of these may be mentioned sulphonol, which is mildly antiseptic, and ichthyol, which is a compound containing as much as 10 per cent. of sulphur, and has enjoyed some reputation as a mild antiseptic lotion.

¹ Harnack, Erich: Schmiedeberg's *Arch.*, Vol. XXXIV., p. 156, 1894.

CHAPTER XLVIII.

PHOSPHORUS AND THE PHOSPHORUS COMPOUNDS.

I.

Historical.

Phosphorus was first discovered by Brandt, in 1669, in the residue from the evaporation of urine. Tunnicliffe¹ states that it was a century later before phosphorus was shown to be present in the bones. Phosphorus plays a most important physiological rôle in the mammalian body. It is a constituent of the most vitally necessary substance of the nucleus, nucleo-protein, also of the phosphatids which serve so important a function in the process of nutrition of the young oviparous and ovoviviparous animals. Milk for the nourishment of the mammalian young also contains phosphorus in abundant quantities in the casein, and as salts of phosphorus. Here, as in the case of iron and sulphur, we find that the problem of the metabolism of phosphorus is of importance primarily to physiological chemistry. Still the influence of the substance on the body has both a toxicological and a pharmacological interest.

Phosphorus is not tolerated by the body, except in combined form, i.e., as organic or as inorganic phosphates. If therapeutic quantities of free phosphorus be taken by way of the mouth, the substance is absorbed and slowly oxidized to the acid. The acid then forms salts with calcium, magnesium, or potassium. But very minute quantities are toxic. On the other hand, both inorganic and organic phosphates are constituents of every normal mixed food. The inorganic phosphates are constantly being excreted, chiefly through the urine. Phosphates are found to be necessary constituents of the food of both plants and animals. Plants are able to take up and utilize inorganic phosphates, deriving them from the soils and the soil waters. It is not so clear to what extent animals may utilize inorganic phosphates. That they do utilize organic phosphates has been clearly demonstrated, a point that will be discussed a little later.

¹ Tunnicliffe, F. W.: *Archives internationales de Pharmacodynamie et de Thérapie*, Vol. XVI., p. 207, 1906.

II.

Outline of Pharmacological Action.

1. *Phosphorus is a general protoplasmic poison.*
2. *It is characterized by excessive nitrogen elimination and by fatty degeneration.*
3. *It interferes with specific functions, largely through derangement of general metabolism.*
4. *Inorganic salts of phosphorus are non-toxic, but are available for the production of bone and stimulate bone growth.*
5. *Organic phosphorus compounds are stimulative to general metabolic processes; they favor the utilization of nitrogen and the growth of muscular, glandular, and nervous tissues.*

III.

Details of Pharmacological Action.

1. **Phosphorus as a general protoplasmic poison.**—The element phosphorus is intensely toxic to animal tissues. This substance has been of interest for the last half century owing to the fact that it is a constituent of the preparation used in the manufacture of matches. Ordinary match heads contain from one to three milligrams of phosphorus. Workers exposed to the phosphorus fumes and dust are subject to definite types of phosphorus poisoning. These present pictures of marked change in the calcareous structure of the bones, as well as of the teeth, produced by the absorbed phosphorus. They also are subjected to a condition of respiratory irritation affecting the mucous membrane down relatively deep into the lungs. Phosphorus in this form is a vigorous irritant. If it be taken into the stomach the irritative change leads to an inflammatory condition of the mucosa, with accompanying griping pains, and generally with vomiting.

All three of these lines of toxic influence show that uncombined phosphorus is poisonous to protoplasm. If the reaction throughout the body is followed, it is found that practically all tissues yield to its influence. The changes in the tissues are essentially of a pathological nature, beginning with absorption of water, cloudy swelling, disintegration, and ultimately fatty degeneration. According to Lusk,¹ the reaction is characterized by an increase in total metabo-

¹ Lusk, Graham: *American Journal of Physiology*, Vol. XIX., p. 461.

lism, as indicated by an increase in total nitrogen eliminated. There is also an excretion of lactic acid, which indicates interference with carbohydrate combustion.

2. **Fatty degeneration after phosphorus poisoning.**—The administration of pure phosphorus has long been used to demonstrate the phenomenon of fatty degeneration. In the beginning the assumption was that phosphorus poisoning led to a breaking down of the protoplasm and to the formation, from its residue or during the process of its disintegration, of fat. In more recent years important and crucial tests have been made casting doubt upon the truth of this assumption. The question hinges on whether or not the observed disintegration of the proteins, which process is associated with an increase of nitrogenous wastes, leads to the formation of fats from the fatty or from the carbonaceous residues, thus accounting for the accumulation of visible fats in certain organs; or whether the fatty accumulations in phosphorus degeneration, so-called, are only transferences of fat from other depots. Two methods have more recently proven fruitful in attacking the problem. Taylor¹ found that frogs, in which he produced fatty degeneration, contained less total fat than the normal controls. By the current theories, there should have been a gain rather than a loss of fat. Rosenfeld² attacked the problem from two angles. He demonstrated first that the increase of fat in the liver is associated with a decrease in the amount of fat in other fat depots of the body. His second point of attack hinges on the fact that the type of fat of each animal is characteristic. By feeding tallow, which is easily identified in comparison with dog fat, and at the same time producing phosphorus poisoning, Rosenfeld found that so-called fatty degenerated liver fat was composed of a high percentage of the foreign fat. Rosenfeld came to the conclusion that the fatty degenerations of this type are in reality fat transportations and do not arise in a breaking up or disintegration of the tissues.

As a result of the tissue disintegration by phosphorus poisoning, there is a temporary increase in the formation of tissue enzymes, of which it is safe to assume lipase is one. An increase of the lipase sets up a series of interdependent physiological conditions, which quite adequately explain many of the cases of fatty accumulation in pathological degenerations, of which phosphorus poisoning is one.

¹ Taylor, A. E.: *Journal of Experimental Medicine*, Vol. IV., p. 399, 1899.

² Rosenfeld: *Verhandlungen der deutschen pathologischen Gesellschaft*, Vol. VI., p. 71, 1904.

As Lusk has stated the case, "the sugar-hungry cells attract fat in greater quantity than they can burn," a statement that calls for a mechanism of lipase for the manipulation of the fats.

3. **The action on the skeletal structures.**—The toxic action on the bony tissues was already mentioned. If phosphorus is given in



FIG. 70.—Comparison of the humerus of a calf to show the influence of phosphorus feeding. *A*, section of the normal bone. *B*, after eight weeks of phosphorus feeding. There is little difference in the thickness of the shaft, but a marked increase of the ossifications around the ends of the epiphyses. The spongy bone is greatly increased and extends further into the shaft. From Wegner.

sufficiently small doses through a considerable interval of time it produces a profound effect on the structural characteristics of bone. Phosphorus at first stimulates to bone formation. Evidently the activity of the osteoblasts is increased so that the laying down of bone, especially in young animals, takes place more rapidly than usual. In the long bones the denser portion of the shaft becomes relatively thicker,¹ and the cancelous tissue extends further down

¹ Wegner, Geo.: Virchow's *Archiv für Anatomie*, Vol. LV., p. 11.

the shaft, and the lamellæ are thicker. The bone formation stimulated by phosphorus does not lead to a greater bone length. In the late and toxic stages of the administration there is a tendency to resorption of the bone salts, which finally weakens the bones and makes them more fragile. There are many points at present not fully explained as regards the toxic action of phosphorus, but apparently we are to look for the source in the interference with the metabolism of the bone-forming cells.

4. **The relations of the inorganic phosphates.**—Aside from the toxic actions of pure phosphorus, the chief interest relates to the rôle and fate of its compounds in the body. Forbes¹ has recently reviewed this problem. He indicates that the organic compounds only are available for most of the tissues, but that the inorganic compounds can be utilized by such tissues as are particularly rich in this group of phosphates. The bones serve as the most typical example. Milk also contains a high percentage of inorganic phosphates. The usual salts are calcium, magnesium, iron, sodium, and potassium phosphates. The mineral bases form strong compounds, and are not readily displaced by the organic bases. On the other hand, organic phosphorus compounds contain a ready phosphorus supply, though an expensive one, for the inorganic uses of the body, especially where an adequate supply of mineral base is present (Forbes).

With these principles in mind, it is evident that one of the most important influences of inorganic phosphates is that on bone metabolism. In the growth of bone the chief mineral constituent is calcium phosphate. If calcium and phosphate salts are not both present, then they must be supplied from their organic compounds or else malnutrition of bone results, i.e., osteomalacia, rickets, etc.

Table showing the percentage of the constituents of the ash of the femur (Carnot).

	Man.	Ox.
Calcium phosphate.....	87.45	85.72
Magnesium phosphate.....	1.57	1.53
Calcium fluoride.....	.35	.45
Calcium chloride.....	.23	.30
Calcium carbonate.....	10.15	11.96
Iron oxide.....	.10	1.13

Inorganic phosphates serve two purposes, therefore they form a direct supply of mineral nutrients for inorganic phosphate purposes;

¹ Forbes, E. B.: Bulletin of the Ohio Agricultural Experiment Station, No. 201, p. 121, 1909.

and they, as with inorganic iron, are phosphorus sparsers. They conserve to the organism for the more complex reactions the higher compounds of the lecithins, nucleo-protein, etc. Forbes, feeding pigs with different phosphorus compounds in the supplement ration, found that raw bone meal and bone flour "increased the density, the volume, and the ash per cubic centimeter of volume, of the bones." There was no obvious advantage in muscular development.

In the Rocky Mountain and western region of the United States, where alfalfa forms the winter ration for the great sheep flocks, it has been noted that the young lambs in utero grow such large skeletons that many are killed at birth.¹ Alfalfa has the largest mineral content of the vegetable feeds. It is particularly rich in calcium, potassium, and phosphorus, as well as in protein. The phosphorus stimulates to greater bone growth, especially in the presence of an abundance of mineral bases, of which calcium is of the chief importance in this instance. A favorable combination in the feeds of protein with the saline substances produces in addition to the skeletal growth an unusual mass development of the soft tissues.

5. Organic phosphorus compounds.—It is well established that organic phosphorus compounds are necessary for the growth and activities of all the tissues of the animal body. Deficiency in this element in organic form leads quickly to malnutrition, and in extreme cases malformation. The most abundant organic phosphates in the foods are: (1) phosphatids, the lecithins; (2) phospho-proteins, of which the casein of milk is an example; and (3), the nucleo-proteins, always present in the cell nuclei as compounds of nucleic acid. Representatives of these classes of organic phosphates are all available, both for the organic and the inorganic phosphorus supply.

The brain is especially rich in phosphorus, 3.7 to 4 per cent. and more, chiefly present in the glycestro-phosphoric acid of the brain lecithins. It is to be expected that interference with brain metabolism will occur if there is a dearth of organic phosphorus in the food supply. Under these circumstances one cannot escape the inference that phosphorus compounds are very vital to the reactions of the brain, including those processes in which conscious thought have their physiological foundations.

Organic phosphorus stimulates growth. Tunnicliffe found that the addition of the phosphorus of a casein and a sodium glycestro-phosphate preparation to the diet of two children was followed by an increase

¹ Unpublished results used by permission of President H. J. Waters of the Kansas State Agricultural College.

in the amount of phosphorus assimilated and retained in the body. There was also an increase in the amount of the food nitrogen assimilated, a fact that had been previously demonstrated. It is this favorable stimulation of metabolism that has given lecithins and the caseins such a strong position among the food drugs.

The nucleo-proteins are also stimulative, but not to a favorable increase in constructive metabolism. The nucleins lead to a leucocytosis, or increase in the number of white blood cells. This is followed by a rise of the amount of phosphorus excreted greater than can be accounted for by the nuclein phosphorus given.

CHAPTER XLIX.

ARSENIC AND ANTIMONY.

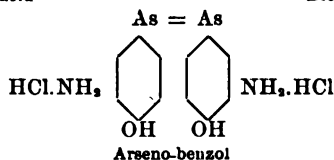
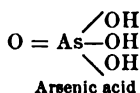
A. ARSENIC.

I.

Introductory and Historical.

The pharmacological importance of arsenic received a new impetus when Ehrlich introduced synthetic compounds of arsenic as specific poisons for certain infectious organisms. The element arsenic is non-toxic as such. The metal is non-soluble in water, therefore cannot be absorbed from the alimentary canal. Arsenic compounds, especially the trioxide, the arsenites, and the sulphites, are peculiarly toxic to all forms of living matter. This toxicity has been known for many centuries. At the present time arsenic is used extensively in the arts. This gives opportunity for accidental poisoning. For example, Paris green, which is an arsenite of copper, and arsenate of lead are the chief insecticides used in vegetable and fruit gardening. Where such vegetables or fruits are carelessly prepared for food opportunity is given for arsenic poisoning. Arsenic is also present as an impurity in certain of the chemicals used commercially, for example sulphuric acid, a fact which gives secondary opportunity for arsenic poisoning.

The compounds of special interest are arsenious acid and its oxidation product, arsenic acid. Of the numerous synthetic arsenic compounds which have been introduced into medicine the more important are atoxyl, or sodium arsanilate, $C_6H_4(NH_2).(AsO.OH.ONa) + 3H_2O$; cacodylic acid, $(CH_3)_2AsO.OH$, and salvarsan, or arsenobenzol, $HCl.NH_2.OH.C_6H_3.As:As.C_6H_3.OH.NH_2.HCl + 2H_2O$.



II.

Outline of Pharmacological Action.

Arsenic compounds interfere with metabolism, hence

1. *Arsenic is a general protoplasmic poisoning.*
2. *The systemic effects are largely secondary to toxic derangement.*
3. *In minute quantities arsenic is stimulative to growth.*

III.

Details of Pharmacological Action.

1. **General toxicity of arsenic compounds.**—Arsenic acid is one of the most toxic of the forms in which arsenic is administered to the body, and it will serve as a type for the discussion of further details. Arsenic poisoning leads to a chain of obscure symptoms which have their expression through the perverted functions incident to general toxic action on the tissue protoplasm. For example, arsenic acid, which is dissolved with difficulty and ionizes slowly, leads to a slow poisoning of the cellular protoplasm. The toxic symptoms come on so slowly and are so obscure that diagnosis is difficult. Even in the acute cases this statement holds. The effects last for long periods, and chronic arsenic poisoning persists for weeks after the cessation of the drug. Where arsenic is used as a cosmetic and the administration oft repeated, pronounced chronic effects may arise and be far advanced before they are identified.

The phenomenon of arsenic poisoning may be divided into stages, of which the first consists only of general weakness associated with derangement of nutrition. The person does not desire food and the food that is taken is imperfectly digested, and there may be a marked disturbance of the alimentary canal accompanied by diarrhea.

A little later, when the arsenic has acted more generally throughout the body, there is swelling of the mucous surfaces, including the membranes of the respiratory tract, of the alimentary tract, and the uro-genital system.

The epidermis is also markedly affected. Sometimes actual disintegration takes place. Usually there is an increase in pigmentation, and the skin becomes noticeably darker. In this stage arsenic is to be found in the skin and skin appendages, and it can be easily identified chemically from the hair.

In the later final stages of chronic poisoning there is paralysis

of the neuro-muscular mechanisms. There is also a disturbance of the sensory side of the nervous system. Inflammation occurs, whereby the ordinary normal physiological sensory responses are greatly exaggerated. There is a tingling and stinging sensation in the skin, especially in the extremities.

Localized areas often give rise to acute pains. The muscular disturbances are associated with paralysis of the motor nerves, in which case the muscles themselves tend to degenerate. General incoördination of locomotor activity is, therefore, characteristic of the late chronic stage.

2. Action of arsenic on the circulatory system.—While arsenic must be classed as a general poison, its influence on the circulatory system creates a pronounced secondary effect on other portions of the body. In the early chronic stage of arsenic poisoning there is a certain degree of edema. This can best be explained on the assumption that the endothelial linings are directly affected by arsenic to such an extent as to interfere with their normal resistance. While the extremely minute dose may stimulate endothelial activity, the toxic reactions lead to degeneration. There is, therefore, a loss of tone in the smaller blood-vessels, especially of the capillaries, with a corresponding dilation.

Arsenic acid is toxic to the heart. If isolated hearts, either of the lower vertebrates or of mammals, be perfused with a solution containing this drug, both the rate of contractions and the amplitudes are diminished. Only a very small margin of drug concentration exists between that strength which will reduce the rate of the heart and that which will completely eliminate its rhythm. The heart will recover readily from a short period of action, but prolonged contact with the arsenic is severely toxic. The action is primarily on the cardiac muscle.

3. The action of arsenic on the alimentary tract.—The acute toxic action of arsenic on the alimentary tract produces a vigorous enteritis. The symptoms appear early. The mucous membrane of the stomach shows the usual inflammatory condition with redness and congestion. The process is slower than with the ordinary corrosives, yet there is undoubted degeneration of the lining epithelium, accompanied by the usual change in resistance. The inflammation may take the form of a violent enough gastritis. The reflexes then produce vomiting, marked increase in the secretions, and often an increase in the intestinal peristalsis. Where the action is intense there is also a fall of blood-pressure with symptoms of shock.

On the intestine arsenic leads to a paralysis of the capillaries with corresponding congestion. A reduction of epithelial resistance occurs, thereby increasing the loss of fluids from the epithelium into the cavity of the canal. If the corrosion is intense and prolonged, then there may be shedding of the epithelium. This adds to the exudates, and in association with the increase in peristalsis contributes to the so-called "rice water" stools, which are characteristic of this form of poisoning. The local action along the alimentary canal is so acute that the whole process often becomes decidedly violent. If so, the final death may come on rapidly because of extreme exhaustion.

In the milder arsenic toxication the action on the alimentary mucous membrane is less intense. There often is a slow chronic degeneration of these cells associated with similar degenerative stages in other parts of the body. The condition comes on so gradually that the acute phenomena just described are passed over and the opposite state of a sluggish and inert canal, i.e., a condition of general constipation, may be the prominent picture.

4. Arsenic on metabolism.—With arsenic compounds, as with the phosphorus compounds, minute doses are at first beneficial in their influence on protoplasm. For example, there is an increase in the growth of the epidermal structures, a laying down of fat in the subdermal adipose tissues, and apparently a favorable reaction on the neuro-muscular tissues. This influence, as also in the case of phosphorus, quickly passes into the toxic injurious stage. In the toxic stage practically all the tissues undergo degeneration in some degree. The typical pathological picture induced is one of an initial cloudy swelling, followed either by inflammation or by rapid disintegration. In the nervous tissues these stages first produce a hypersensitiveness, then later paralysis. In the glandular tissues there is an increase of secretion followed by degeneration and loss of secretory power. In the alimentary canal the phenomena have already been given above. In the liver, however, there is at first an increase in the formation of bile, but later a marked degeneration of the parenchyma. In the skin the increased growth is followed by pigmentation and then by degeneration, and in the kidney a mild nephritis, followed by degeneration with suppression of the urine.

5. The excretion of arsenic.—Arsenic is excreted in practically all of the secretions of the body, particularly in the secretions of the skin, namely, the sweat and milk, and of the kidney. Some arsenic is lost by way of the alimentary canal, but most of it is thrown off through the urine. Arsenic is only slowly excreted. Following a

single dose the process of excretion may last through ten or twelve days. In fact, it has been observed in the urine as high as 160 days after the last administration. Evidently the drug is stored in the different organs of the body in a form from which it is only slowly liberated and finally thrown off.

IV.

Organic and Synthetic Arsenic Compounds.

Reference was made in the introduction to the work of Ehrlich in deriving the synthetic arsenic compound salvarsan. The general toxicity of arsenic led Ehrlich to the special attempt to build up arsenic compounds of reduced toxicity to the tissues of the host while retaining the usual toxic action for invading organisms. Ehrlich's ambition was to secure a selective antiseptis by this means. The organic arsenic compounds, namely, cacodylic acid and arsanilic acid, have long been known to possess a high degree of toxicity for certain pathogenic germs. Ehrlich developed a series of instructive and valuable synthetic products by the attachment of arsenic to various derivatives of the benzene ring compounds.

6. **The arsanilates.**—Arsanilic acid is a compound produced from arsenic acid, in which aniline takes the place of one hydroxyl. Various metallic salts are derived from arsanilic acid, producing arsanilates that have been introduced into *New and Non-official Remedies* under special names, usually proprietary. Sodium arsanilate (atoxyl), $C_6H_4(NH_2).(AsO.OH.ONa) + 3H_2O$, is described by the 1914 edition of *New and Non-official Remedies* in the following terms: "The arsenic of the arsanilic acid is liberated very slowly in the system, thus producing the ordinary therapeutic effects of arsenic, with a more continuous and less toxic action and less irritation. Toxic effects from excessive doses have been frequently noted, although the toxicity of sodium arsanilate is stated to be about 1-40 of that of arsenic trioxide. The poisonous effects appear to be due largely to the arsenic component, the aniline taking no part in them. It is claimed that the use of sodium arsanilate is not followed by irritation, abscess formation, etc., which sometimes follow the use of other preparations of arsenic. The use of sodium arsanilate in large doses has occasionally been followed by degeneration of the optic nerve, leading to blindness.

"Sodium arsanilate has been recommended for the conditions which are favorably influenced by arsenic, such as anemia, nervous conditions, and diseases of the skin. It is said to have been very success-

ful as a remedy for trypano-somiasis, both of animals and of man, and is also said to be useful in other protozoal diseases, such as syphilis, malaria, and kala-azar."

The importance of this anilin arsenic compound is in association with its toxicity for the infectious organisms, such as in syphilis, malaria, etc. In the body the compounds break up, liberating arsenic in such form as to be specifically toxic for the invading organism. It was at first thought that this compound was not toxic for the body tissues, but numerous cases have arisen leading to disintegration and loss of function of special structures, the most distressing of which is that of blindness from degeneration of the optic nerve.

7. **Salvarsan.**—At this point may be discussed the synthetic work of Ehrlich in the building up of compounds with a maximum of toxicity to invading organisms, associated with a minimum of toxicity for the tissues of the host. Ehrlich has exhaustively considered this question on theoretical grounds. His views led him to construct numerous synthetic compounds, some of which he has shown to be practically selective in their toxicity for invading organisms. In 1910 the medical world was electrified by the announcement of a compound, number 606 of his series, which was specifically toxic for the spirillum of syphilis. This compound is arseno-benzol, or salvarsan. It presumably owes its action to the special form in which the arsenic is carried.

The serum studies which have led to the development of special means of detecting invading organisms have given practical diagnostic signs for many of our most dreaded diseases, the Wiedal reaction for typhoid, the tuberculin reaction for tuberculosis, and the Wassermann reaction for syphilis. By the application of the specific syphilitic test it is now possible to determine positively whether or not the body of a given individual has been invaded by this dreaded organism. The arsenic treatment, through the specific salvarsan, is borne especially well by the body in which the spirillum is present. Some condition developed by the spirillum seems to make the body tolerant of the arsenic compounds in this form. This tolerance is greater than that possessed by the normal body, hence in practical treatment the safe method is first to determine the presence of the organism by the Wassermann reaction and then give the specific salvarsan in the belief that the tissues will resist the toxic substance and the invading organism will succumb without danger to the host.

Ehrlich has announced the almost unbelievable result that after single injections of salvarsan the invading organisms completely dis-

appear. Numerous clinical treatments in Europe and in America have abundantly established the specific value of this agency along clinical lines.

B. ANTIMONY.

Antimony, which is the chemical relative of arsenic, has also been used in medicine for many years. Like arsenic, antimony is generally toxic and more or less irritant to the tissue cells. The form used in medicine is tartrate of antimony or tartar emetic.

1. **The irritant action of antimony.**—Antimony is far more directly irritant than arsenic, and therefore can be used externally as a skin irritant and internally as a strong gastric irritant. It is this last factor which has given to the compound the name of tartar emetic. The application of antimony to the skin leads to local inflammation. Around the mouths of the sweat glands and the sebaceous glands, where the drug is absorbed more deeply, it tends to produce pustules. This reaction produces stimulations of the nerve endings, reflexes which are discussed more fully under the head of Counter Irritants.

Antimony given internally in relatively small doses, 30 mgr., produces at once an acute irritation of the lining of the stomach. This irritation also leads to vigorous nerve reflexes. The result is an increase of the secretions, both salivary and gastric, in the milder stages of its actions, and nausea and vomiting in the more intense stages. This function of inducing vomiting is the one that has been most used in therapeutics.

Antimony is not so readily absorbed as some drugs, unless by mischance there be gastric ulcer or other form of abraded surface. The systemic effects of antimony are toxic, somewhat comparable to arsenic in this regard. There is, therefore, danger of nervous, of vascular, and other disturbance of vital functions, such as occasionally lead to severe and dangerous collapse.

Antimony is primarily excreted with the feces, but it is present in traces in the secretions. The antidote is tannic acid, which forms an insoluble precipitate, in which form it can be removed from the stomach by the usual methods of lavage.

CHAPTER L.

LEAD SALTS.

I.

Historical and Chemical.

Lead is a toxic metal, the salts of which vary in virulence very largely in proportion to their solubility in water and in the body fluids. The salts of especial interest are the insoluble salts, such as litharge, or lead monoxide, PbO , sulphate PbSO_4 , carbonate, or white lead, PbCO_3 , and the iodide, PbI_2 . The important soluble salts of lead are the nitrate, $\text{Pb}(\text{NO}_3)_2$, and the acetate, $\text{Pb}(\text{C}_2\text{H}_3\text{O}_2)_2$, or sugar of lead, is the most soluble of all, and is the salt most used in practical therapeutics. Lead salts are of chief pharmacological interest because of the great intensity of their toxic action, rather than because of their value in therapeutic practice.

II.

Outline of Pharmacological Action.

The reactions of lead in the body may be summarized as follows:

1. *General toxicity to protoplasm because of the formation of lead protein compounds after absorption.*
2. *A characteristic astringent action of the dilute salts.*
3. *Concentrated lead salts are irritative, and hence produce local inflammation.*
4. *There is a strong tendency to chronic irritation after prolonged absorption of minute quantities.*

III.

Details of Pharmacological Action.

1. **The general toxic action of lead salts.**—Lead salts owe their toxicity primarily to the fact that they precipitate proteins. The formation of lead protein compounds in the protoplasm of the cells destroys the normal power of physiological reaction of the tissues

concerned. This statement holds whether the action be on free mucous surfaces or on abrasions, as in the use of lead salts as astringents. The reactions are the same when the salts have entered the circulation and reached the tissues by the paths of general distribution. The toxic picture, as expressed through changes in the coördinations throughout the body, varies, therefore, according to the degree of poisoning on one or the other tissue, as the case may be.

The insoluble salts are not absorbed unless they be converted while in contact with the moist tissues into soluble forms, as happens typically with the lead carbonates. Most soluble lead salts, like salts of mercury, penetrate the tissues comparatively rapidly. When a solution of a salt of lead is taken into the stomach, it begins at once to diffuse through the mucous membrane. However, it quickly forms a superficial layer of insoluble lead protein; in other words, produces a tanning effect on the surface layers of the mucosa. In consequence of this initial action the further absorption of lead is delayed, though not prevented. The intensity of the local action of lead depends largely on the concentration of the solution. If the dilution is great, then there will be only a local astringent action. If the concentration is medium, the astringent action will pass over into a definite irritation that will involve the sensory nerve endings, which will in turn lead to reflex changes in secretion, peristalsis, etc. The solutions of greater concentration lead to an immediate irritative process and acute toxic action, which produces nausea and vomiting, and ends in acute inflammation.

When the lead salts reach the intestines the cycle of changes which have been described for the stomach are repeated. The more rapid absorption from the intestinal region induces a greater intensity of local action. This local action affects the vascular channels, producing a stricture of the blood-vessels, which takes the character of a vascular spasm, therefore producing an asphyxial condition of the tissues of the regions supplied. The direct lead action on the smooth muscle of the intestinal walls produces prolonged contractions, with the griping pains which characterize the so-called lead colic.

In acute lead poisoning, this cycle of symptoms may occur within a very short period, i.e., within a few hours. Systemic effects not mentioned but associated with acute lead poisoning are great thirst, nervous distress, and prostration, sluggish circulation, with cold extremities. In the later periods of the cycle a suppression of the urine sometimes occurs, and there are general muscular cramps, which may end fatally in convulsions or in paralysis. As a rule, however, this

extreme acute toxicity does not occur, and the victim may slowly recover even after large doses of sugar of lead, the most soluble of the lead salts.

The obvious antidote for acute lead poisoning is administration of an indifferent sulphate or carbonate, such as sodium sulphate or carbonate, with the hope that the soluble lead may be converted into an insoluble salt, and in that inert form be eliminated from the body.

2. Chronic lead poisoning.—Acute lead poisoning, as described above, is rare as compared with the number of cases of chronic lead poisoning. Lead in one form or another is used very extensively in the arts, and, as may be expected, chronic lead poisoning, therefore, is commonly found among painters, lead workers, plumbers, glass workers, and pottery glaziers. Lead may enter the body by inhalation from the dust, may be absorbed through skin abrasions, but it is more commonly taken up by slow and continual absorption from the alimentary canal after entrance by way of the mouth. Drinking water may contain lead from lead pipes, foods also preserved in lead sealed containers may be the source of lead intoxication, but uncleanness in handling lead-containing substances is the usual source of intoxication.

The slow and continual absorption of lead gradually introduced into the general circulation and distributed throughout the body is the most common history of lead poisoning. The reaction with protein renders it difficult of excretion, therefore there is a gradual and accumulative action. The acute or local symptoms may be entirely absent, but in due time general toxic symptoms make their appearance. The more common introductory symptom is acute intestinal cramps, i.e., "lead colic." This is followed, after a few days or weeks, often without other premonitory warning, with muscular paralysis. It is an interesting observation that the paralysis most always affects the nerves of the upper extremities, beginning at the points of distribution of the nerves to the muscles of the fingers, hand, and arm. Muscular control is lost in a definite order. The first affected are the extensors of the middle fingers, then of the thumb and little finger, and then gradually of the wrist, leading to the characteristic "wrist drop." The attack is usually, but not always, bilateral, and gradually extends to other muscles. The fuller details of this condition may be had from more extensive works on toxicology. Other nerve symptoms are due to the loss of sensory functions.

The organs of excretion, especially the kidney, and to less extent the salivary and other glands of the alimentary tract, are strongly affected in chronic lead poisoning. Early nephritis occurs, followed by marked degeneration and necrosis of the nephridial tubules.

3. **The action of lead on the digestive tract.**—Under the heading of the toxic action of lead we have already discussed some of the changes produced on the alimentary tract. However, further emphasis should be given to the fact that the gastric and intestinal symptoms represent a complex, not only due to local action, but to special action after absorption. For example, the intravenous injection of lead salts produces diarrhea and the characteristic lead colic. Diarrhea from this method of treatment is accompanied by violent intestinal muscular spasms. The muscular walls do not completely relax, but persist in clonic contraction. In fact, in the chronic stage the intestinal spasm loses more and more its peristaltic character, and hence constipation becomes a constant and persistent symptom from the peculiar type of interference with the normal movements of the intestinal tube.

It is not fully clear whether the intestinal spasms are due to the direct stimulation of the smooth muscle, as such, or to primary action of the lead on the local nervous mechanism. If one may draw conclusions from evidences of the toxic nature of the lead reactions in other parts of the body, he would infer that the nerve explanation was the more probable. During the muscular spasm of the intestine there is also a marked spasm of the blood-vessels, which produces a local asphyxiation contributory to the general toxicity.

4. **Excretion of lead by the salivary and intestinal glands.**—Lead is excreted to a slight extent by the salivary glands. It is present in the saliva and the mouth in quantity sufficient to produce the characteristic blue line along the teeth near the margin of the gums. The insoluble lead sulphide is formed and deposited at this region, especially if any uncleanness of the teeth exists.

The glands of the stomach and of the intestines also excrete lead salts. In fact, the mucosa itself possesses this function, accounting, in part, for the final loss of lead through this channel. But in this instance, as in the case of morphine, there is a considerable reabsorption of the lead, which establishes a vicious circle. This fact contributes to the difficulties with which lead is finally and entirely excreted from the body.

5. **Excretion of lead by the kidney.**—The major portion of the lead is slowly excreted by the kidney. It is the excretion by this organ

that brings the toxic metal in intimate contact with the nephridial epithelium, hence the result is more or less disastrous. The situation is very similar to that of the excretion of the salts of mercury. There is a tendency toward protoplasmic precipitation, which leads to acute inflammation or nephritis, and this is followed by parenchymatous necrosis. Profound functional disturbance is inevitable. A voluminous urine of low specific gravity characterizes the early stages of the disease, uremia and dropsy the later chronic stages.

6. **The reaction of lead on the circulatory system.**—After the absorption of lead into the blood stream it tends to react both with the constituents of the blood and with the lining epithelium of the blood-vessels. As a result of the former reaction there is some change in the character of the blood plasma. It is true that this leads to only secondary stages in lead poisoning. The chief damage to the blood falls upon the white corpuscles and the erythrocytes. The white corpuscles lose their ameboid character, become sluggish, and tend to disintegrate, hence their activities are reduced below the normal. Disintegration of the red corpuscles, with a tendency toward the formation of methemoglobin, has been described. This process leads to a reduction of the percentage amount of respiratory pigment, and there follows the chain of symptoms expressed by anemia and malnutrition. The reaction of lead salts on the epithelium of the blood-vessels produces a toxic condition which, when prolonged, leads to two unfavorable symptoms. The first of these, which arises early, is characterized by a tendency to contraction or spasms of the arterioles and capillaries. The second and later symptom is characterized by developing arterio-sclerosis, with the secondary accompanying symptoms, which that term implies.

Various interferences with the normal rhythm and force of the heart's contraction have been ascribed to the effect of lead salts. However, lead only slowly combines with striated muscle substance, of which cardiac muscle is a type. After prolonged action there is a tendency to muscular weakness and cardiac paralysis, quite comparable to the chronic changes in skeletal muscle.

7. **The reaction of lead on the nervous system.**—Harnack¹ also made a study of the influence of lead on the nervous system of frogs and mammals. It is to his classical work that we owe our experimental conception of this field. He found that lead salts after ab-

¹ Harnack, E.: *Archiv für experimentelle Pathologie und Pharmakologie*, Vol. IV., p. 152, 1878.

sorption produced strong initial stimulating effects on certain centers of the nervous system. These facts were demonstrated through the muscular responses given by dogs. In determining the action on the blood vascular system it was found that lead salts injected into the circulation after section of the cervical sympathetic nerve on one side produced general blood vascular spasms. The contractions were stronger on the unoperated side, showing that lead stimulated the vasomotor center as well as the smooth muscles of the vessels. In the later or chronic action of lead, this nervous reaction becomes toxic, producing paralysis of certain nerve centers. The paralysis is not specific and varies much in different individuals. It is this toxic effect on the cortical areas which constitutes the *encephalopathia saturnalis*. As a result of the cortical disturbance there is a marked interference with the psychic factors as expressed by restlessness, occasional delirium, usually followed in the end by marked depression and central paralysis.

In closing the discussion, one may emphasize the fact that secondary physiological effects of lead poisoning produce variations in the primary symptoms. The uremic convulsions, which follow the destruction of the renal function, will suffice as a single example of such secondary results.

The peripheral nerves are poisoned in the later stages of lead action. In fact, the most typical phenomenon of lead poisoning, namely wrist-drop, is due to paralysis of the motor nerves rather than of the muscles concerned. The action is not directly upon the motor nerve ending, but upon the axis cylinders along the course of the nerves.

8. Muscular effect of lead poisoning.—Harnack's classical picture of the effects of lead on striated and other muscles shows a marked interference with the typical muscular contraction and the expenditure of muscular energy. His diagrams indicate a very characteristic onset of fatigue with a minimum of recuperative power, also a typical arrest of the relaxation phase at the last third. This change in a way resembles that which characterizes veratrine, but it does not come so early in the relaxation.

This phenomenon was observed in the muscles of frogs and rabbits, and it involved the striated skeletal and cardiac muscles. As the lead action proceeded the muscle substance lost its irritability and finally became paralyzed, or at least unresponsive. Strange to say, the muscles of the dog were, in Harnack's hands, quite immune from these typical changes.

That there are additional factors involved has been shown by Cash.¹ Cash studied lead muscular poisoning under the influence of variations in temperature. At temperatures of from 15.5° to 17° C. the muscles did not give the characteristic lead contractions. At temperatures of 30° C. and more the lead poisoned muscles did give this result. Cash came to the conclusion that for some unknown reason the combination of lead with the muscular substance is prevented by certain unfavorable temperatures and favored by others.

Cardiac muscle seems to fall into the same class as skeletal muscle, so far as lead action is concerned. We find the heart, therefore, contracting more feebly and at a slower rate, and with a tendency to prolonged diastole. However, the heart responds to its nerves so long as its muscle remains sensitive to direct stimulation.

Smooth muscle also is changed by the formation of lead proteins in its protoplasm. This is indicated by Harnack's experiment quoted above on the circulation in the ear of the rabbit after the section of the vasomotor nerves. The contraction of the blood-vessels on the isolated side can only be explained as a direct muscular effect. This view is strengthened by the actions on the alimentary canal, which have been discussed above.

¹ Cash, Th.: "Archiv für Experimentelle Pathologie und Pharmakologie," Supplementband, Schmiedeberg's *Festschrift*, p. 93, 1908.

CHAPTER LI.

ZINC SALTS.

I.

Details of Pharmacological Action.

The zinc salts, that are of interest in a pharmacological way, are the oxide ZnO , the sulphate ZnSO_4 and the chloride ZnCl_2 . The oxide is insoluble, while the sulphate and chloride are very soluble, therefore the more readily absorbed by the mucous membrane of the alimentary canal.

1. **General toxic and disinfectant action of zinc salts.**—The salts of zinc precipitate proteins as in the case of the lead salts. The formation of insoluble albuminates on protoplasmic surfaces gives to the zinc salts their characteristic astringent property. Zinc albuminates are even less soluble than lead albuminates. When the action is more intense, as in the more concentrated solutions of zinc, the effect on protoplasm is merely irritant. Zinc chloride being more soluble, therefore penetrates more readily into the tissues, hence it is the more irritant of the zinc series. The chemical action of zinc on protoplasm gives to its salts their antiseptic property. Zinc chloride enters into the composition of special disinfectant solutions such as in Pott's solution.

2. **The local action of zinc salts.**—In the human body the local application of zinc salts produces its effects according to the surface involved. The skin is non-absorbent, therefore zinc salts have little or no influence. The more soluble and stronger salts, as for instance zinc chloride, will produce local inflammation, but this comes on slowly and is insignificant unless prolonged. On the other hand, the comparatively insoluble zinc oxide is only a mildly antiseptic and stimulative medium, since just sufficient of the salt is dissolved to produce this general effect. It therefore finds a use in clinical medicine as a healing salve to cover exposed and ulcerating surfaces.

3. **The systemic action of zinc after absorption.**—The more soluble zinc salts are slowly absorbed from abraded surfaces, and particularly by the alimentary mucosa. Yet it is claimed that direct cases of chronic zinc poisoning are rare, if not entirely absent.

However, if a solution of a zinc salt is introduced into the circulation, a procedure that can be accomplished by using some one of the double salts of zinc which does not so readily precipitate protein, a cycle of symptoms follows directly due to the toxic action of the metal. It has long been known that zinc sulphate is an emetic. In the earlier history of medicine a solution of this salt was a favorite medium for the production of vomiting. In this instance the explanation is that the zinc, after absorption, directly stimulates the nerve centers concerned in vomiting. With excessive and toxic doses death follows, primarily through the paralysis of the nervous system and of the cardiac muscle.

Take it all in all, the zinc salts are considerably less toxic than the salts of lead. For therapeutic purposes they are relatively unimportant.

CHAPTER LII.

THE SALTS OF COPPER.

I.

Details of Pharmacological Action.

The salts of copper, like those of lead and zinc, enter into combination with protein. This reaction is the foundation of such toxic effects as they produce on animal and plant tissues. The copper salts are relatively soluble. The ones most commonly met with in pharmacological experiments are copper sulphate, copper acetate, and the double salts of copper and arsenic, as the copper arsenite.

1. **General toxic and disinfectant action of copper salts.**—Living tissues respond with great variation to contact with solutions of copper salts. This may be explained in part by the fact that copper is normally present in a number of plants and in certain animal tissues. As an example, it is a well-known fact that copper takes the place of iron in the respiratory pigments of some lower forms of animals. The blood of certain species of crustaceans, of which the common edible crab is an example, and of certain molluscs, contains the respiratory pigment hemocyanin, which differs chemically from hemoglobin in that copper displaces the iron of the pigment molecule. Fredricq¹ has shown that hemocyanin chemically unites with oxygen in a very unstable combination, comparable with that of oxygen and hemoglobin. The oxyhemocyanin, however, is of a pale blue color instead of the usual scarlet red, which characterizes oxyhemoglobin.

It has been shown also that certain plants contain traces of copper. However, numerous observations also show that many of the lower plant forms are very susceptible to the toxic action of copper. This fact is taken advantage of in the practical purification of water supplies, especially in the ridding of reservoirs of the infesting fresh water algæ. Minute traces of copper, such as are given to the water by dragging a sack of copper sulphate through a reservoir, are sufficient to kill the *spirogyra* and other species of pond algæ.

Locke has shown that copper salts are toxic to lower forms of

¹ Fredricq, L.: *Archives de Zoologie Experimentale*, 1878.

animal life. As dilute a solution as one in two hundred thousand is sufficient to kill ciliated infusoria and isolated ciliated epithelial cells.

On the other hand, the tissues of man and mammals are relatively resistant to the toxic action of copper sulphate. Certain tissues withstand, for a short time, as high a concentration as one per cent., though this concentration finally becomes toxic. Some molds are said to be resistant to copper, while certain yeasts are very susceptible to its action, though copper sulphate is the principal ingredient of the well-known Bordeaux mixture which is used as a spray to rid plants of fungus diseases.

2. **Systemic symptoms of the action of copper.**—Copper salts owe their toxicity to the formation of protein compounds, just as in the cases of lead and zinc. This property gives them the usual astringent action, and with sufficient concentration an irritant and corrosive toxic end result. Copper is an old-time emetic, depending upon its irritation of the mucous lining of the stomach. It produces nausea with pain from local irritation. After absorption the salts react chiefly on the nerves and muscles to produce an increase in the respiratory rate and a slow weak pulse accompanied by dizziness and ending in paralysis or sometimes convulsions.

Copper salts are not so toxic as lead salts, in fact chronic action does not often, if ever, occur. That the continued use of applications is detrimental cannot be questioned. Its irritant action on the alimentary tract when often repeated, as in the use of foods preserved with copper cooked in copper vessels, have a tendency to produce a gastric and intestinal catarrh and a chain of secondary symptoms depending thereon.

3. **The elimination of copper salts.**—Copper salts are comparatively easily absorbed from the alimentary tract. They are distributed by the blood throughout the body. The liver has been found to contain a higher percentage of copper, though traces have been observed in most every tissue. The metal is slowly eliminated through the excretory glands, especially the kidney. However, traces of copper have been found in the excretions of the skin and in the hair. It is re-excreted into the alimentary canal to a certain extent, chiefly by the salivary and digestive glands. A portion of the copper is discharged from the body in the feces.

CHAPTER LIII.

THE MERCURY SALTS.

I.

Introductory.

Mercury is one of the most active of the heavy metals. It is toxic in the body, not only from the action of the ions derived from the salts, but following the absorption of the metal itself. The most common salts of mercury used for pharmacological and medicinal purposes are: Mercuric chloride, HgCl_2 , mercurous chloride, Hg_2Cl_2 , mercuric iodide, HgI_2 , and the metal itself.

II.

Outline of Pharmacological Action.

The most important changes in the behavior of living protoplasm introduced by mercury are:

1. *Mercury has a cathartic action on the alimentary canal.*
2. *Salts of mercury are highly toxic for micro-organisms.*
3. *In very dilute solutions, as one in three hundred thousand or less, salts of mercury are stimulative to protoplasm, producing an increase in the red blood cells, diuresis, etc.*
4. *Salts of mercury, in the more concentrated solutions, are very toxic for animal and vegetable protoplasm.*

III.

Details of Pharmacological Action.

1. **The absorption of salts of mercury.**—The extraordinary toxicity of mercury depends primarily upon two factors: (1) The relative solubility of its salts as compared with other heavy metals; (2) the solubility of its protein compounds in animal fluids. Of the different mercury salts calomel or mercurous chloride is comparatively insoluble. When it is introduced into the alimentary canal it only slowly dissolves, and is correspondingly slowly absorbed.

This accounts for the fact that relatively large quantities of this salt may be swallowed with impunity, since they pass through the canal without being absorbed. Mercuric chloride, on the other hand, is highly soluble and correspondingly toxic.

Whenever mercury is brought into contact with either the fluids of the body or the tissues, it enters into chemical combination with the protein constituents forming protein compounds. Proteins are in this way precipitated, but the precipitate, when in small amount, is readily soluble in excess of fluid largely on account of the sodium chloride content of the body fluids. Mercury, therefore, present in the mammalian body takes the form of albuminates. These, in solution, pass readily to all parts of the body and lead to the characteristic mercurial action. This action is merely stimulative when the substance is present in extremely diluted solution, i.e., traces, but strongly corrosive when the concentration reaches the toxic level.

The action of the metal mercury follows when the substance enters the body either by absorption of its vapor through the pulmonary tracts or by absorption from the skin when the metal is applied in the form of a fine emulsion, as in inunction of mercurial ointment.

2. The action of mercurial salts on bacteria and other lower forms of life.—Mercury has come to be recognized as one of the most valuable of the antiseptic substances. Its soluble mercuric chloride is the form used for the purpose of antiseptics and disinfection. It has a powerful and toxic action on the lower forms of living matter. For purposes of disinfection, the bichloride in solutions of one part in one thousand is the strength generally used. For the disinfection of excreta and other highly infectious substances, other chemicals are probably more available, but a solution of bichloride of mercury one part in one thousand will kill all active forms of bacteria if allowed to stand in contact a sufficient length of time. For many bacteria, one part in a million will inhibit growth. Other forms of bacteria, of which the tubercle bacillus is an example, are more resistant to the action of mercuric chloride. Even one in one thousand must stand in contact with tubercle bacilli for several hours to insure their death. Resting spores are naturally more resistant and require a more vigorous treatment for sterilization, if it be produced by solutions of mercury.

In surgical procedure, the antiseptic action of mercuric salts is relied upon at the present day, where asepsis is not practical. The solutions, from the standpoint of the human patient, are bland and

not acutely irritant, hence not painful. However, in surgical dressing it must be remembered that the tissues of the body are also susceptible to local mercurial poisoning. A prolonged contact with stronger antiseptic solutions may lead to superficial irritation and possibly necrosis and death of the cells of the area.

Soluble mercuric salts are also toxic to generalized protoplasm, such as infusoria, white blood corpuscles and the like. A solution of one in ten thousand is sufficient to inhibit the movement of white blood corpuscles. This fact can be demonstrated in the incipient stage of inflammation produced by mercuric chloride. An inflammatory process in the frog's web, started by mercuric chloride solution, will exhibit the fact that the white corpuscles have lost their migratory powers.

3. The action of mercury on differentiated animal protoplasm. —From what has been said above, it is evident that mercuric chloride solutions have a varied action on the individual tissues of the animal body. In concentrated solutions this action is a toxic one, while in the very diluted solutions just the opposite, i.e., a temporary beneficial and stimulative effect, may be seen. The concentrated solutions convert enough of the protein of the tissues into the albuminate to destroy the characteristic cell life. On the other hand, the extremely diluted solutions do not bring to the tissues enough of the mercurial salts to immediately produce destruction of the tissues. In the latter case a very slight formation of albuminate in the protoplasm has the rather unexpected effect of increasing the activity of the tissues concerned. It is obvious that the increase of functional activity in certain tissues will have secondary effects that are more or less favorable to the organism as a whole. If the intensity of action is toxic and tissue-necrosis occurs at any point, then the elimination of function of that tissue will lead to secondary actions that are, in the nature of the case, injurious to the life of the organism as a whole. One need only to refer to the fatal necrosis of the kidney in chronic and fatal mercurial poisoning as an example. The favorable action of minute quantities of mercury has been taken advantage of by clinicians in certain pathological conditions, for example in anemia following infectious disease.

Fortunately the margin of safety between the concentration of salts of mercury which is toxic for the body tissues and that which is toxic for the invading bacteria attacking those tissues is great enough to allow of the use of the drug as an antiseptic. This factor

is particularly applicable for cutaneous surfaces because of the resistance which the skin offers to absorption. If an abrasion exists, as in the case of an ulcer, or following a surgical operation, or if mucous surfaces of the body are to be disinfected with mercurial salts, as in the case of the mouth cavity, the rectum, or the vagina, then care must be taken lest excessive absorption occur and the body receive a toxic quantity of the drug. Keeping in mind these general factors, we may examine next the action on particular organs in the body.

4. **The action of salts of mercury on the alimentary tract.**—Salts of mercury have long enjoyed a favorable reputation because of their cathartic action. Calomel, or mercurous chloride, because of its relative insolubility and correspondingly slow absorption rate, serves as a splendid cathartic. Mercuric chloride is violently irritant to the alimentary tract, but is available as a purge where it is desirable to use only an intense acting drug. The cathartic action of calomel depends upon the fact that it is slowly dissolved. Its concentration is ordinarily never great enough to produce more than a mild irritation before it is absorbed from the alimentary tract, hence produces a relatively mild cathartic action. The local inflammation which it induces in the mucous lining produces only a slight amount of exudation, which is favorable from the standpoint of a cathartic. The cathartic action of calomel often fails of the final defecation reflex, hence leads to an accumulation of refuse in the large intestine.

Mercuric chloride is violently irritant. It leads not only to local inflammation, but induces vigorous reflexes, beginning with those from the gastric cavity. As a result the salivary and gastric secretions are increased and there is a tendency to nausea and vomiting. If the action is strong enough, there is an interference with the circulation and respiration, and if extremely severe collapse may supervene. This last extreme is usually not reached.

With toxic quantities of mercuric chloride, as in the case of accidental poisoning from corrosive tablets, there is rapid absorption and enough mercury enters the system to produce acute poisoning. In such cases, the poisonous action is prolonged and death follows from the continued contact with mercury at the points of excretion, particularly in the colon and in the kidney.

5. **Action on the central nervous system.**—Salts of mercury are relatively inactive so far as the function of the central nervous system is concerned. Even in toxic quantities, when the poisonous effects proceed to the climax in death, consciousness continues until

the last. Certain nervous derangements do occur after prolonged mercurial poisoning. There is an increased irritability to sensory stimulation, a degree of loss of muscular control shown by the feeling of muscular fatigue and by mercurial palsy. As in lead poisoning the muscular disturbances usually appear first in the upper extremities and extend thence over the body. Other local nervous symptoms have been described in chronic mercurial poisoning, but they are not of sufficient constancy to be enumerated in this connection.

6. **The action of mercurial salts on the circulatory and respiratory systems.**—Of all the parts of the body, the least to be affected are the organs of the circulation. The nerve control of the heart and blood-vessels remains intact to the last. The same is true for respiration. Such derangements as occur are primarily due to muscular disturbance in the later toxic action. Experiments indicate that the heart, at least of the frog, responds with a more favorable rhythm and force in the presence of very dilute solutions of mercuric chloride. Strips of cardiac muscle, ventricle of the terrapin, contracting in physiological solutions, withstand the action of one in one thousand solutions of mercuric chloride many minutes, maintaining a very uniform rhythm and only slowly decreasing the amplitude as the muscle protoplasm is slowly coagulated by the mercuric salt.

7. **Action of mercury on the kidney.**—The kidney, of all the organs of the body, is one of the most susceptible to mercurial salts. This is no doubt due to the condensation of mercury in the nephridia during the process of excretion. Both the glomerulus and the secreting tubules are sharply affected. The toxic action takes the form of irritation, followed by inflammation. There is an early suppression of the excretion of urine, accompanied by the presence of blood products in the urine, i.e., red corpuscles, albumin, and in many cases sugar. As the inflammatory process continues, the renal parenchyma undergoes necrosis, and a deposit of calcium salts may take place both in the cells and in the cavity of the tubules. Such a pathological condition is accompanied by complete anuria leading to uremia.

Very minute quantities of mercury are stimulative to urinary secretion. This has been shown by Cohnstein¹ on rabbits. He found that an intravenous injection of calomel leads to an increased secre-

¹ Cohnstein, W.: *Archiv für Pathologie und Pharmakologie*, Vol. XXX., p. 132, 1892.

tion of urine; a fact that has been often observed clinically after the administration of the salt.

The effect of intravenous injection of mercurous chloride on the secretion of urine in the rabbit (Cohnstein).

PERIOD OF SECRETION.	Amount of urine per ten minutes.	
	Rabbit No. 16.	Rabbit No. 17.
1. Normal.....	.15 cc.	1.01 cc.
2. ".....	.18 cc.	0.87 cc.
3. ".....	.16 cc.	0.87 cc.
Dose Hg ₂ Cl ₂ in jugular.....	.01 cc.	.004 cc.
4. Mercury.....	9.21 cc.	3.09 cc.
5. ".....	4.47 cc.	5.95 cc.
6. ".....	2.75 cc.	5.96 cc.

These experiments indicate an increase in the secretion of urine of from one to six and more, per unit of time.

This effect on the kidney is probably due to direct stimulative action of small quantities of mercury on the renal epithelium, an action which can and does readily pass over to one of toxic injury as expressed in inflammation and necrosis. A different explanation has been offered, namely, that the great fluidity of the intestinal content in the region of the large intestine leads to a hydremia, and that this condition indirectly stimulates the kidneys to a greater secretion.

8. The excretion of mercury.—The formation of albuminates of mercury tends to the storage of this metal in the body tissues. The complete secretion of mercury, therefore, takes place only after a long interval. Indeed, mercury may be found in the excretions of the body for months after its last administration. However, the elimination of mercury begins within a few minutes after its absorption and its slow excretion continues until its ultimate removal. The channels by which the mercury leaves the body are the alimentary canal on the one hand, and the kidney and skin on the other. All intestinal and cutaneous glands excrete mercury. It is thought that the greater portion leaves the body by way of the kidney, except in cases of extreme cathartic action. This statement applies, of course, only to mercury after absorption. The large amount lost by way of the alimentary canal after absorption is that thrown off in the secretion of the salivary, gastric, and pancreatic glands, and by the intestinal mucosa itself. It is generally claimed that the mucosa excretes a large percentage of the

salts of mercury. Mercury, as was found to be the case also with lead, detected in the epithelial cells of the colon and rectum is considered to be excretion mercury, not mercury in the process of absorption.

A number of the local effects of mercury, especially observed in chronic mercurial poisoning, are due to its condensation at the point of excretion. Salivation is an example, as is also mercurial nephritis, and the ulceration that occurs in the lower bowel and at points on the skin.

9. **Acute toxic action of mercury.**—Cases of mercurial poisoning are more or less common, and generally arise from the actions of the soluble mercuric chloride or corrosive sublimate. The solubility of this salt and the rapidity with which it is absorbed accounts for the chain of symptoms which characterize the condition. The primary effects are due to the local irritation of the alimentary tract. There is acute gastritis accompanied by nausea, usually vomiting and diarrhea with intense griping pains. If the inflammation has progressed far enough the vomit will contain flecks of blood, and sometimes disintegrated epithelium from the corrosion of the mucous membrane. The stools are usually voluminous and watery, and may also contain, besides the usual fecal matter, disintegrated epithelial tissue. These symptoms occur almost immediately, certainly within a few hours. If the corrosion is unusually severe there is a degree of collapse from the extensive visceral reflexes.

The acute symptoms occurring from action of mercury after absorption are those which might be expected from the coagulation of the protoplasm of the tissues in various portions of the body. The most important of all is acute nephritis with suppression of the urine. A weak and irregular heartbeat also follows, with low blood-pressure, and an increase in the secretion of saliva and of perspiration. While there may be muscular weakness, the general muscular and nervous reactions are little if at all interfered with.

10. **Chronic mercurial poisoning.**—Chronic mercurial poisoning, called mercurialism, occurs after prolonged absorption of the salts of mercury. This class of toxic action is rendered more common because of the widespread use of mercury in the treatment of syphilis and other venereal infections. The early symptoms are found in inflammation of the mouth, including the gums, and an increase in the secretion of saliva or insalivation. The inflammatory process about the gums may progress to an actual necrosis, beginning

in the bone around the bases of the teeth and involving more or less of the jawbones.

The alimentary canal shows the effect of the poison especially along the lengths of the intestine, particularly the large intestine. This usually takes the form of chronic diarrhea. The concentration of the action at this point is presumably associated with its excretion here.

Other regions through which mercury is excreted begin to show the effect of its toxic action. For example the irritant effect on the skin leads to local foci of an erythematous type of inflammation, usually in association with the sweat glands. This is to be attributed to the direct action of the mercury as a result of the cutaneous excretion.

The chronic effects of mercury on the kidney have already been indicated. Following the acute suppression of function and the beginning of renal inflammation, there is a progressive degeneration especially of the secreting cells of the convoluted tubules. The glomeruli are also involved in this necrosis. When the lesion is extensive enough, it leads to a failure to excrete the waste products of the body, and therefore to general toxic uremia and death. It is evident that a poison so toxic in its action will produce an inevitable depression of metabolism. This is shown in the general weakness and in the final anemic condition of the victim.

CHAPTER LIV.

SALTS OF SILVER.

I.

Details of Pharmacological Action.

Silver nitrate has long been extensively used for medicinal purposes, but in recent years has been more or less displaced by a number of organic silver compounds. Of the organic compounds, the silver vitellate and silver caseinate are soluble in water and not precipitated by the albumin or the chlorides of the blood.

1. **The local and antiseptic action of silver salts.**—For many years the fused silver nitrate crystals have been used locally as a caustic for mucous surfaces and especially for local infections. When a cauterizing stick is applied to a mucous surface, the nitrate crystals begin to dissolve and to form a surface film of albuminate. The action is strongly antiseptic, destroying the infectious bacteria as well as the surface albumin. The irritant action of silver nitrate depends upon the formation of this local eschar. Silver, like lead, prevents its own rapid and extensive absorption by the process of precipitation of albumin. But silver is more irritant than lead, though less astringent.

Solutions of silver nitrate are disinfectants for mucous membranes. They have been used especially to combat local infection of the mouth and throat, for the disinfection of the eyes and rather extensively for the disinfection of the uro-genital apparatus.

The soluble organic preparations of silver are not precipitated by albumins and are non-irritant. Therefore, a higher percentage of silver may be brought in contact with surfaces in this form.

2. **The toxic action of silver salts.**—Silver poisoning by the accidental swallowing of lunar caustic or from the accidental injection of silver nitrate has occurred. Crystallized nitrate in the stomach dissolves rapidly and forms extensive local lesions. These are accompanied by a precipitation of albumin over the surface of the mucosa. This is followed by inflammation with intense burning pain, and still later by extensive corrosion, which may terminate

fatally. A fatal case from 30 grains taken by an adult has been reported, while half that quantity swallowed as lunar caustic proved fatal in a child of fifteen months.

The accidental subcutaneous injection of a four per cent. solution of silver nitrate is reported to have been accompanied by intense burning pain, followed in a couple of hours by more general deep-seated pains associated with the bones of the neighboring parts. In twenty-four hours the injected tissues appeared pale and began to slough. Extensive inflammation occurred in the neighboring tissues and extended for some distance along the lymphatic channels. Healing in such cases is extremely slow, apparently from interference with a sufficient vascular supply.

3. Systemic effects.—The general systemic effects of silver are not extensive. This is due to the formation of soluble silver compounds and the elimination of this salt from toxic activity. If given by way of the mouth, silver solutions are in part transformed into insoluble lead sulphides and are lost with the feces. Absorption albuminates are formed, converting the silver to a less active form. Certain toxic nerve effects have been described. The spinal cord and the medulla are slightly stimulated at first, then general paralysis is produced. The various automatic centers in the medulla are involved in this process, especially the vasomotor, cardio-inhibitory, and the respiratory centers. Cohnstein describes a striking increase in renal secretion in the rabbit after ten milligram doses of silver chloride in solution in sodium hyposulphite given subcutaneously. In one experiment the urine per hour was increased from 1.64 to 11.60 grams; in another experiment from 1.50 to 6.39 grams. He records only a trace of albumin in the urine in a single experiment. However, silver salts have not been described as excreted by the urine.

Silver that has been absorbed becomes fixed in various organs, particularly in the connective tissues and muscles, where it is precipitated in insoluble form. In the continued clinical use of silver salts it has been known for many years that precipitation of the silver in the connective tissues leads to a permanent pigmentation. Extensive deposits of silver take place in the subdermal connective tissue, giving to the unfortunate a peculiar bluish color known as argyria. This pigmentation is permanent, at least we have found no means for its removal up to the present time, unless the solvent action of hexamethylamine, described by Dr. Crispin, proves the efficient agent (see note, page 337).

CHAPTER LV.

SALTS OF BISMUTH.

I.

Details of Pharmacological Action.

Bismuth is still another heavy metal that possesses therapeutic interest of high degree. The soluble salts of bismuth are readily absorbed and toxic. These are the bismuth salts of certain inorganic acids, especially bismuth ammonium citrate. The insoluble salts bismuth subnitrate, subcarbonate, also bismuth subcitrate as well as certain other bismuth organic compounds that are not soluble in water, are only slightly soluble in the body fluids. These salts are non-toxic.

1. **The action of soluble bismuth compounds.**—Soluble bismuth compounds are toxic after introduction into the system, and poisonous effects are similar to that of certain other heavy metals, perhaps to mercury more than to any other. In the nervous system the toxic action falls heavily on the spinal cord and medulla. The symptoms are those of strong stimulation accompanied by rapid respiration, by muscular cramps, and generally by vomiting, later by motor paralysis and consequent suppression of respiration. The action on the circulatory system affects primarily the cardiac muscle, leading to weak circulation. In the symptoms of salivation and stomatitis, comparable to that of mercurialism which has been described, there is a tendency to diarrhea with ulceration and often necrosis of the large intestine, and to nephritis.

The toxic action of bismuth sometimes appears from the extensive application of insoluble salts to ulcerating surfaces. This undoubtedly depends upon some unknown condition favoring solution and absorption of the basic compounds.

2. **The action of insoluble bismuth salts.**—The insoluble bismuth salts have, in recent years, widely extended use, especially in connection with the study of the alimentary tract by the Röntgen-ray method. Bismuth subnitrate, which is the usual salt used for this purpose, is very opaque to the rays, hence gives a sharp picture of

the boundaries of the alimentary cavities. Difficult physiological problems as regards the alimentary movements have been explained by this method. Notable among these are the studies of Cannon¹ on the movements of the stomach and of the intestines. Preparations of the bismuth subnitrate are also used for certain Röntgen-ray pictures of the uro-genital apparatus, particularly of the ureters and of the pelvis of the kidney. No untoward results come from this treatment, either in man or mammals.

The subnitrate of bismuth is absorbent. When brought in contact with the living tissues, as in the case of the surface of an ulcer or the mucosa of the alimentary canal, it acts as an absorbent and a mild antiseptic. The antiseptic properties are due to the solution of traces of the bismuth. This is explained by the solvent action of the tissue fluids. In the case of the stomach, if there is an excessive secretion of hydrochloric acid in the gastric juices, a portion of the subnitrate will be reduced, giving rise to a small amount of bismuth chloride. The subnitrate remaining insoluble is carried forward along the canal by the peristalses. The traces of soluble salts are absorbed and enter the circulation and are excreted by the kidney.

When bismuth subnitrate passes the cecum it meets and reacts with the sulphides, which are present in greater or less quantities in the large intestine, thus forming bismuth sulphide. The sulphide has a toxic influence, not only on the mucosa, but on the capillaries and smaller blood-vessels of the intestinal wall. Whether the bismuth sulphide acts to obstruct the circulation by small thrombi, as has been claimed, or by other toxic influences, it results in a tendency to ulceration with necrosis in local areas. In general, bismuth has a slight sedative influence on the movements of the alimentary canal, probably due largely to the reduction of the subnitrate by such salts as sodium sulphate, thus eliminating the stimulative effects of the sulphate ion. Bacteria, which produce fermentation in the large intestine of the animal body, have a tendency to liberate nitrites from the bismuth subnitrate, a process that has been described by Böhme.² He found in tests on the rabbit that after the introduction of subnitrate of bismuth into the loop of the large intestine the urine of the animal reacted strongly to tests for nitrites

¹ Cannon, W. B.: *The American Journal of Physiology*, Vol. I., p. 359, 1898; Vol. VI., p. 251, 1902.

² Böhme, A.: "Über Nitritvergiftung nach interner Darreichung von Bismuthum subnitricum," *Archiv für experimentelle Pathologie und Pharmakologie*, Vol. LVII., p. 441, 1907.

within a few hours. He also showed that nitrites could be detected in the blood of the animal. The toxic influence of nitrites from this source are sufficient to produce death of an animal (see nitrites, page 178).

DOSE TABLE FOR THE MORE IMPORTANT DRUGS NOW IN USE.

The following Dose Table contains the average individual doses and the maximum doses. The average dosage is taken from *Useful Remedies*, compiled by the Council on Pharmacy and Chemistry of the American Medical Association, and published by the American Medical Association Press. The maximum dosage is taken from William Wood and Company's *Physician's Diary for 1914*.

APPENDIX.

Adult Doses (by the mouth)

DRUG.	Average Dose.		Maximum Dose.	
Acetanilide	0.25 gm.	4 gr.	0.50 gm.	8 gr.
Acet-phenetidin ...	0.5 gm.	7.5 gr.	1.00 gm.	15 gr.
Acid. aceticum dil..	4.00 cc.	1 dr. (Troy)
Acid. benzoicum ...	0.5 gm.	7.5 gr.	2.00 gm.	30 gr.
Acid. boricum	0.5 gm.	7.5 gr.	1.00 gm.	15 gr.
Acid. carbolicum	0.13 gm.	2 gr.
Acid. citricum	0.5 gm.	7.5 gr.	2.00 gm.	30 gr.
Acid. hydrochlori- cum dil.	1.00 cc.	15 min.	2.00 cc.	30 min.
Acid. hydrocyanicum dil.	0.1 cc.	1.5 min.	0.20 cc.	3 min.
Acid. salicylicum ..	0.5 gm.	7.5 gr.	1.30 gm.	20 gr.
Acid. tannicum	0.5 gm.	7.5 gr.	0.65 gm.	10 gr.
Aconiti tinctura ..	0.6 cc.	10 min.	0.30 cc.	5 min.
Aconitina	0.00026 gm.	1/250 gr.
Adrenaline, 1/1000. (See epinephrine)	0.5 cc.	7.5 min.	1.00 cc.	15 min.
Æther	1.00 cc.	15 min.	4.00 cc.	1 fl. dr.
Ætheris nitrosi spir- itus	2.00 cc.	30 min.	8.00 cc.	2 dr. (Troy)
Ætheris spiritus ...	4.00 cc.	1 fl. dr.	6.00 cc.	1.5 dr. (Troy)
Ætheris spiritus compositus	4.00 cc.	1 fl. dr.	6.00 cc.	1.5 dr. (Troy)
Aloe	0.250 gm.	4 gr.	0.65 gm.	10 gr.
Aloes extr.	0.125 gm.	2 gr.	0.65 gm.	10 gr.
Aloes tinct.	8.00 cc.	2 dr. (Troy)
Aloin	0.065 gm.	1 gr.	0.20 gm.	3 gr.
Ammoniacum	2.00 gm.	30 gr.
Ammoniae spiritus..	4.00 cc.	1 dr. (Troy)
Ammonii chloridum	0.5 gm.	7.5 gr.	0.65 gm.	10 gr.
Ammonii phosphas.	1.30 gm.	20 gr.
Amyl nitris	0.2 cc.	3 min.	0.30 cc.	5 min.

382 DOSE TABLE FOR THE MORE IMPORTANT DRUGS NOW IN USE

Adult Doses (by the mouth).—Continued.

Drug.	Average Dose.		Maximum Dose.	
Antimonii et potas- sii tartras (emet- ic)	0.03 gm.	0.5 gr.	0.06 gm.	1 gr.
Antipyrin	0.25 gm.	4 gr.	1.00 gm.	15 gr.
Apocynum			1.30 gm.	20 gr.
Apomorphinæ hydro- chloras (emetic) ..	5 mg.	0.1 gr.	0.006 gm.	0.1 gr.
Argenti lactas			0.32 gm.	5 gr.
Argenti nitras	0.01 gm.	0.5 gr.	0.06 gm.	1 gr.
Arsenii iodidum			0.01 gm.	1/6 gr.
Aspirin	0.5 gm.	7.5 gr.	2.00 gm.	30 gr.
Atophan			1.00 gm.	15 gr.
Atropinæ sulphas ..	0.4 mg.	1/160 gr.	0.00065 gm.	0.01 gr.
Barii chloridum ...			0.065 gm.	1 gr.
Belladonnæ foliorum tinct.	0.5 cc.	8 min.	1.00 cc.	15 min.
Belladonnæ radix ...			0.06 gm.	1 gr.
Benzoini tinct.			2.00 cc.	30 min.
Bismuthi citras			0.30 gm.	5 gr.
Bismuthi subnitras ..	0.5 gm.	7.5 gr.	2.00 gm.	30 gr.
Caffeina	0.065 gm.	1 gr.	0.20 gm.	3 gr.
Caffeina citrata ...	0.125 gm.	2 gr.	0.32 gm.	5 gr.
Caffeinæ sulphas			0.30 gm.	5 gr.
Calcii chloridum ...	0.5 gm.	7.5 gr.	1.30 gm.	20 gr.
Calcii hypophosphis ..	0.5 gm.	7.5 gr.	1.00 gm.	15 gr.
Calomel	0.065 gm.	1 gr.	1.30 gm.	20 gr.
Camphoræ spiritus ..	1.00 cc.	15 min.	2.00 cc.	30 min.
Cantharis			0.03 gm.	0.5 gr.
Cantharidis tinct. ...			0.65 cc.	10 min.
Cascara sagrada ext. ...			0.50 gm.	8 gr.
Chloral	1 gm.	15 gr.	2.00 gm.	30 gr.
Chloretone			0.65 gm.	10 gr.
Chloroformum	0.15 cc.	2 min.	0.65 cc.	10 min.
Chichonæ tinct.	4.00 cc.	1 fl. dr.	8.00 cc.	2 fl. dr.
Coca			8.00 cc.	2 gr.
Cocainæ hydrochlo- ras	0.03 gm.	0.5 gr.	0.13 gm.	2 dr. (Troy)
Codeina	0.03 gm.	0.5 gr.	0.65 gm.	1 gr.
Conine			0.006 gm.	0.1 gr.
Copaiba	1.00 cc.	15 min.	2.00 cc.	30 min.
Creosotum	0.2 cc.	3 min.	0.30 cc.	4 min.
Cupri arsenitis			0.0006 gm.	0.01 gr.
Cupri sulphas (emetic)	0.25 gm.	4 gr.	0.32 gm.	5 gr.
Curare			0.006 gm.	0.1 gr.
Digitaline (cryst. Nativelle)			0.002 gm.	1/30 gr.
Digitalis extr. fl. ...			0.12 cc.	2 min.
Digitalis tinct.	1.00 cc.	15 min.	1.30 cc.	20 min.
Elaterium	0.005 gm.	0.1 gr.	0.004 gm.	1/16 gr.

Adult Doses (by the mouth).—Continued.

Drug.	Average Dose.		Maximum Dose.	
Emetina (alkaloid)			{ 0.002 gm. to 0.02 gm.	{ 1/30 gr. to 1/3 gr.
Epinephrine, 1/1000	0.5 cc.	7.5 min.	1 cc.	15 min.
Ergota fl. ext.	2.00 cc.	30 min.	4.00 cc.	1 dr.
Eserina			0.0013 gm.	1/50 gr.
Eserinæ salicylæ	0.001 gr.	0.065 gr.	0.003 gm.	1/20 gr.
Eucainæ hydrochloras β.			2.00 cc.	30 min. 6% sol.
Ferri arsenas			0.006 gm.	0.1 gr.
Ferri chloridum			0.25 gm.	4 gr.
Ferri chloridi tinct.	0.5 cc.	8 min.	2.00 cc.	30 min.
Ferri et quininæ citras			0.65 gm.	10 gr.
Ferri et strychninæ citras			0.12 gm.	2 gr.
Frangulæ extr. fl.			2.00 cc.	30 min.
Gaultheriæ oleum			1.00 cc.	15 min.
Gelsemina (alkaloid)			0.003 gm.	1/29 gr.
Gelsemii extr. fl.			0.65 cc.	10 min.
Gentianæ extr.	0.25 gm.	4 gr.	0.65 gm.	10 gr.
Glonoïn			0.001 gm.	1/60 gr.
Heroin	0.003 gm.	0.05 gr.	0.01 gm.	1/6 gr.
Homatropinæ hydrobromas	0.0005 gm.	1/128 gr.	0.003 gm.	0.05 gr.
Hydrargyri chloridum corros.	0.003 gm.	1/20 gr.	0.006 gm.	0.1 gr.
Hydrargyri massa	0.250 gm.	4 gr.	0.40 gm.	6 gr.
Hydrastinæ hydrochloras			0.65 gm.	1 gr.
Hydrastis tinct.			4.00 cc.	1 dr. (Troy)
Hyoscine hydrobromas			0.001 gm.	1/60 gr.
Hyoscyaminæ hydrobromas			0.001 gm.	1/60 gr.
Iodi tinct.			0.32 cc.	5 min.
Iodothyrim			1.30 gm.	20 gr.
Jalapæ resina			0.40 gm.	6 gr.
Lithii citras			1.30 gm.	20 gr.
Magnesia	2.00 gm.	30 gr.	4.00 gm.	1 dr. (Troy)
Magnesiæ citras granulatus			30.00 gm.	1 oz. (Troy)
Magnesiæ sulphas	15 gm.	240 gr.	30.00 gm.	1 oz. (Troy)
Manna			30.00 gm.	1 oz. (Troy)
Menthæ piperitis aqua			16.00 cc.	4 dr. (Troy)

384 DOSE TABLE FOR THE MORE IMPORTANT DRUGS NOW IN USE

Adult Doses (by the mouth).—Continued.

DRUG.	Average Dose.				Maximum Dose.			
Mentha piperita spiritus	2 cc.	30 min.			1.00 cc.	15 min.		
Menthol	0.065 gm.	1 gr.			0.065 gm.	1 gr.		
Methylis salicylas ..	1 cc.	15 min.			2.00 cc.	30 min.		
Monobrom - acetanilide					1.00 gm.	15 gr.		
Morphina	0.01 gm.	0.20 gr.			0.03 gm.	0.5 gr.		
Morphina hydrochloras	0.015 gm.	0.25 gr.			0.03 gm.	0.5 gr.		
Morphina sulphas ..	0.015 gm.	0.25 gr.			0.03 gm.	0.5 gr.		
Morrhua oleum	16 cc.	4 fl. dr.			16.00 cc.	4 dr. (Troy)		
Muscarina nitras					0.06 gm.	1 gr.		
Myrrha tinct.	1 cc.	15 min.			1.00 cc.	15 min.		
Naphthol β					0.30 gm.	5 gr.		
Nicotinum					0.001 gm.	1/60 gr.		
Nitroglycerinum					0.001 gm.	1/60 gr.		
Nucis vomica extr.	0.015 gm.	0.25 gr.			0.03 gm.	0.5 gr.		
Nucis vomica tinct.	0.6 cc.	10 min.			1.30 cc.	20 min.		
Opium					0.12 gm.	2 gr.		
Ouabain					0.00026 gm.	1/250 gr.		
Ovarin					0.36 gm.	6 gr.		
Pancreatin	0.5 gm.	7.5 gr.			2.00 gm.	30 gr.		
Papain					0.50 gm.	8 gr.		
Para-acet-phenetidm ..					1.00 gm.	15 gr.		
Pepsinum	0.25 gm.	4 gr.			1.30 gm.	20 gr.		
Phenacetine					1.00 gm.	15 gr.		
Phenol (absolute) ..	0.065 gm.	1 gr.			0.20 cc.	3 gr.		
Phenolphthalein	0.1 gm.	1.5 gr.			2.00 gm.	30 gr.		
Phosphorus	0.5 mg.	1/125 gr.			0.0013 gm.	1/50 gr.		
Physostigmatis extr.					0.006 gm.	0.1 gr.		
Physostigmina sulphas	1 mg.	1/62 gr.			0.0006 gm.	0.01 gr.		
Pilocarpina					0.05 gm.	0.75 gr.		
Pilocarpina hydrochloras	0.01 gm.	0.20 gr.			0.05 gm.	0.75 gr.		
Plumbi acetas	0.065 gm.	1 gr.			0.20 gm.	3 gr.		
Podophyllum	0.015 gm.	0.25 gr.			1.30 gm.	20 gr.		
Podophylli extr.					0.32 gm.	5 gr.		
Podophyllin					0.03 gm.	0.5 gr.		
Potassii acetas	2 gm.	30 gr.			2.00 gm.	30 gr.		
Potassii bromidum	1 gm.	15 gr.			2.65 gm.	40 gr.		
Potassii citras	1 gm.	15 gr.			4.00 gm.	1 dr. (Troy)		
Potassii cyanidum					0.0065 gm.	0.1 gr.		
Potassii et sodii tartras	8 gm.	120 gr.			30.00 gm.	1 oz.		
Potassii iodidum	0.5 gm.	7.5 gr.			1.30 gm.	20 gr.		
Potassi sulphas					16.00 gm.	4 dr. (Troy)		
Quillaia tinct. (1 to 10)					4.00 cc.	1 dr. (Troy)		
Quinina hydrobromas					1.30 gm.	20 gr.		

Adult Doses (by the mouth).—Continued.

Drug.	Average Dose.		Maximum Dose.	
Quininæ hydrochloras	0.25 gm.	4 gr.	1.00 gm.	15 gr.
Quininæ sulphas ...	0.25 gm.	4 gr.	1.00 gm.	15 gr.
Rhamni purshianæ extr. fl.	1.00 cc.	15 min.	16.00 cc.	4 dr. (Troy)
Rhei extr. fl.			2.00 cc.	30 min.
Rosein (Fuchsin) ..			0.25 gm.	4 gr.
Salol			2.00 gm.	30 gr.
Sarsaparillæ ext. fl.			4.00 cc.	1 dr. (Troy)
Scilla	0.125 gm.	2 gr.	0.20 gm.	3 gr.
Scillæ extr. fl.			0.20 cc.	3 min.
Scillæ syr.	2 cc.	30 min.	4.00 cc.	1 dr. (Troy)
Scopolamine hydrobromate	0.5 mg.	1/125 gr.	0.001 gm.	1/64 gr.
Senna	4 gm.	60 gr.		
Sennæ extr. fl.	2 cc.	30 min.	16.00 cc.	4 dr. (Troy)
Sennæ syr.	4 cc.	1 fl. dr.		
Serpentaria			2.00 gm.	30 gr.
Sodii arsenas	5 mg.	0.1 gr.	0.008 gm.	1/8 gr.
Sodii bicarbonas ...	1 gm.	15 gr.	4.00 gm.	1 dr. (Troy)
Sodii bromidum ...	1 gm.	15 gr.	4.00 gm.	1 dr. (Troy)
Sodii citras			4.00 gm.	1 dr. (Troy)
Sodii phosphas	2 gm.	30 gr.	4.00 gm.	1 dr. (Troy)
Sodii salicylas	1 gm.	15 gr.	2.00 gm.	30 gr.
Sodii sulphas	16 gm.	240 gr.	30.00 gm.	1 oz. (Troy)
Strophantin (g) ...	0.3 mg.	1/200 gr.	0.005 gm.	1/12 gr.
Strychninæ nitras..			0.006 gm.	0.1 gr.
Strychninæ sulphas.	1 mg.	1/64 gr.	0.005 gm.	1/12 gr.
Suprarenal gland ..			0.30 gm.	5 gr.
Taraxaci extr. fl. ...			4.00 gm.	1 dr. (Troy)
Terpin hydras	0.125 gm.	2 gr.	1.30 gm.	20 gr.
Theobromine	0.3 gm.	5 gr.	0.30 gm.	5 gr.
Thymol	0.125 gm.	2 gr.	0.12 gm.	2 gr.
Thyroid extract ...			0.50 gm.	8 gr.
Trimethylamina			0.40 cc.	6 min.
Urethane			4.00 gm.	1 dr. (Troy)
Valerianæ extr. fl. ...	2.00 cc.	30 min.	4.00 cc.	1 dr. (Troy)
Veratrina			0.003 gm.	0.05 gr.
Veratri viridis extr. fl.			0.20 cc.	3 min.
Zinci acetas	0.125 gm.	2 gr.	0.12 gm.	2 gr.
Zinci sulphas (emet-ic)	1 gm.	15 gr.	2.00 gm.	0.5 dr.

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